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THE CAUSE OF DEATH IN DIABETES*

A Report of 307 Autopsied Cases

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A SEARCH through the literature for an answer to the question of the causes of death in diabetic patients reveals a large amount of available material, with surprisingly little of it based on pathological confirmation through autopsy examination. Analyses based on clinical findings alone and on diagnoses found on death certificates are filled with patent inaccuracies. Joslin[1] and others have repeatedly demonstrated that figures gathered from death certificates are subject to so many errors as to vitiate many of the conclusions drawn from them. The example of a cerebral hemorrhage found at autopsy as a cause of death in a case clinically diagnosed as a diabetic coma is a not infrequent occurrence. This report therefore represents an attempt to determine the causes of death in a series of diabetic patients from a strictly anatomic approach, comparable to the series of 486 diabetic autopsies reported by Warren.[2] It is believed that such statistical analyses based on anatomic findings give more accurate information regarding causes of death than do analyses based solely on clinical observations.

MATERIAL AND METHODS

The subject matter of this report is drawn from a study of 307 diabetic patients autopsied at the Mallory Institute of Pathology during the years 1932–1942, inclusive. Excluded from the study are a few cases in which the material was inadequate. In each case the complete protocol was reviewed and the available histologic material was examined to establish the anatomic cause of death. When more than one possibility presented itself, the clinical records were reviewed in an effort to understand more clearly the patient's terminal course. It is obvious that cases were met with in which no clear-cut conclusion could be drawn, either because of inadequate records or because of the fundamental limitations of the anatomic approach. Such cases were discarded. The patients included 131 males and 176 females, ranging between the ages of thirteen and eighty-four.

As a basis for comparison, the anatomic causes of death in approximately 2800 autopsied nondiabetic patients were summarized. The control group represented all nondiabetic patients over twelve years of age coming to autopsy in the years 1936, 1937, 1941 and 1942, whole years being selected to avoid seasonal variations. These particular years were selected in an effort to represent both the pre-sulfonamide and post-sulfonamide eras, as well as changing therapies over the period of investigation.

Adequate histologic material was available in 268 of the diabetic cases. Routine sections of the liver, kidneys, pancreas and adrenal glands were studied in an effort to determine the frequency of specific histopathologic changes associated with the diabetes.

RESULTS

Table 1 indicates the distribution of the causes of death in the diabetic and control series. These various groups and subgroups were selected because they obviously represent the most frequent conditions of which diabetic patients — and for that matter nondiabetic ones — die. Certain of the headings used require a few words of explanation to clarify the type of case included within the category.

The term "peripheral vascular disease" is used to indicate the cases of vascular insufficiency leading to gangrene and death, either without infection or with infections so trivial as to constitute only a minor part of the clinical picture. In many of these cases, amputation was performed and was followed at some interval of time by death. If there was a clear-cut chain of circumstance pointing to the peripheral vascular disease as the initiating event in the fatal course, the death was listed in this category. On the other hand, infections of the extremities were separated from the above group because

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it was thought that, despite the underlying vascular insufficiency that some of these patients had, the clinical picture was dominated by the superimposed infection. The patients showed essentially febrile reactions, often with spreading sepsis, septicemia and death.

TABLE 1.

CAUSE OF DEATH	DIABETIC GROUP NO. OF CASES	DIABETIC GROUP PERCENTAGE	DIABETIC GROUP CORRECTED PERCENTAGE*	NONDIABETIC GROUP PERCENTAGE
Coma	22	7.2	—	—
Vascular disease:				
Cardiac decompensation	35	11.4	12.3	12.6
Coronary occlusion	31	10.0	10.8†	4.2†
Cerebral hemorrhage and thrombosis	15	4.9	5.2	7.5
Peripheral vascular disease	13	4.2	4.5†	0.0†
Central (pulmonary embolism)	7	2.3	2.4	2.8
Renal disease:				
Glomerulonephritis	2	0.7	0.7	0.4
Acute pyelonephritis	21	6.8	7.3†	1.6†
Miscellaneous	2	0.7	0.7	2.0
Infection:				
Pulmonary	73	23.8	25.6	24.2
Peritoneal	13	4.2	4.5	4.8
Extremities	7	2.3	2.4†	0.5†
Other infections	22	7.2	7.7	5.9
Cancer	24	7.8	8.4†	14.7†
Other causes (including unknown)	20	6.5	7.0	17.0

*From a statistical viewpoint, in order to compare the diabetic and control groups, it is necessary to eliminate coma cases from the comparison, since they are a hazard peculiar only to the diabetic patient and are not found in a series of control cases. This column, therefore, represents the diabetic series from which coma cases have been excluded, the mortality percentage being recomputed in order that they may be strictly comparable with those of the control group.

†Denotes statistically significant differences.

The term "pulmonary infection" indicates a wide variety of inflammatory diseases of the lung, such as bronchiectasis, lung abscess, pneumonia and tuberculosis, no attempt being made to separate this heterogeneous collection into its component parts.

In the interests of simplicity, unknown causes of death, traumatic deaths, anemias and a diversity of the less frequent fatal diseases have been grouped under the heading "other causes."

The most frequent cause of death in the diabetic group was pulmonary infection (25.6 per cent); cardiac decompensation and coronary occlusion follow with 12.3 per cent and 10.8 per cent, respectively. The relative frequency of fatal carcinoma is seen to be 8.4 per cent. That of acute pyelonephritis, decompensated, was 7.3 per cent, and that of uncomplicated coma 7.2 per cent. Cerebral vascular disease was found to be relatively low in the scale, accounting for only 5.2 per cent of the deaths.

In the control group pulmonary infection again led with 24.2 per cent. Deaths due to carcinoma were second with 14.7 per cent. Cardiac decompensation followed with 12.6 per cent, whereas coronary occlusion and acute pyelonephritis were significantly far down on the list, with 4.2 and 1.6 per cent, respectively.

Table 2 indicates the frequency of certain histopathologic changes in the diabetic group. These lesions were arbitrarily designated as + to ++++, only changes of ++ or greater being considered significant. Evidence of cirrhosis was found in 27 of the 268 cases; the type was alcoholic cirrhosis in 13, biliary cirrhosis in 11, and healed acute yellow atrophy in 3.

Finally, as has been shown before,[3, 4] the average age at death of the diabetic patients in this series was not significantly different from that of the nondiabetic, being 59.6 years in the former and 59.8 years in the latter.

DISCUSSION

In considering the figures presented, one must bear in mind that they are derived from a large municipal hospital, accepting all varieties of cases, many already in terminal or near-terminal stages, together with emergency cases combed from a wide metropolitan area. For example, the apparent high incidence of pulmonary infection as a cause of death as compared with that in other series is due in part to the fact that the hospital annually receives a significant number of cases of pulmonary tuberculosis. In the diabetic group, 17 of the 73 fatal pulmonary infections were tuberculous, representing a frequency of 5.6 per cent or 6.0 per cent when corrected for coma. A comparison with the 8 per cent incidence found in the control group reveals no significant difference between the two groups. Similarly, deaths from coma (7.2 per cent) occupy a higher rank in the causes of death in the present series than that found in other published series because some of the patients were not infrequently first seen in far-advanced coma at a stage in which the process had perhaps become irreversible.

TABLE 2. *Selected Histologic Findings in 268 Diabetic Patients*

LESION	DEGREE OF CHANGE ++++	+++	++	+	NONE	SIGNIFICANT CHANGE %
Kidneys:						
Glycogen nephrosis	17	44	43	14	39	42
Benign nephrosclerosis	29	50	58	19	93	55
Intercapillary glomerulosclerosis	7	23	21	3	201	20
Pancreas:						
Hyalinization or fibrosis of islets	8	24	34	12	106	36
Liver:						
Nuclear glycogen	27	54	60	20	53	66
Fat	13	22	34	30	41	48

On the other hand, the relatively low incidence of coronary occlusion as a cause of death (10.8 per cent) may be in part attributable to two factors. In the first place, in this laboratory the assignment of coronary occlusion as a cause of death is not made unless the myocardial infarction is significantly large, or unless there is a clear-cut terminal clinical course that corroborates the finding of an occluded coronary artery in cases in which the process has been too recent for the development of a massive infarction. In the second place, a certain percentage of acute coronary deaths are handled by the Medical Examiner's Office and hence are not available for inclusion within this series.

Perhaps worthy of emphasis is the finding of a relatively similar incidence of cerebrovascular accidents as a cause of death in the diabetic and nondiabetic groups — 5.2 per cent and 7.5 per cent, respectively. This finding is in agreement with that of Root and Sharkey,[5] who state that the nonmuscular cerebral arteries have no greater predisposition to atherosclerosis in diabetic than in nondiabetic patients.

A point of further interest is that there was a lower incidence of death from carcinoma in the diabetic group (8.4 per cent) than in the control group (14.7 per cent). In view of the close similarity of the survival age in the two groups, age does not seem to aid in accounting for the difference, and at present no other factor appears to be implicated. It is particularly noteworthy in view of the present interest in the relation of cholesterol and of hypercholesterolemic states to the production of neoplasia. A comparison of the figures reveals other significant differences in only four categories, namely, coronary occlusion, peripheral vascular disease, acute pyelonephritis and infections of the extremities.

Considering each of these separately, one finds that coronary occlusion was two and a half times as frequent in the diabetic group as in the control group. Peripheral vascular disease, although a rarity among nondiabetic patients, accounted for 4.5 per cent of the deaths among diabetic patients, which confirms a well-known fact previously emphasized. A similar situation obtains with reference to infections of the extremities, in which the admonitions of Joslin[6] are borne out by the greater frequency with which this complication leads to death among diabetic patients than among nondiabetic ones. Finally, renal infection, which for many years has been considered a minor complication, is seen to be a relatively important cause of death in the diabetic group. Acute pyelonephritis was four and a half times as frequent a cause of death in the diabetic group as in the control group, and moreover ranks sixth among the causes of death in the former group.

The six most frequent causes of death in the two groups are listed in Table 3.

In Warren's series of 486 autopsies on diabetic patients who died during the years 1924–1937, inclusive, coma was present in 127 cases, or 26 per cent. Arteriosclerotic cardiac lesions were the cause of death in 17 per cent of the patients, whereas cerebral arteriosclerosis accounted for 4 per cent of the deaths. The percentage of patients dying of pulmonary infections was 10 per cent, with pyelonephritis occupying a low place on the list of total causes, accounting for only 2 deaths.

TABLE 3. *Most Frequent Causes of Death in Diabetic and Nondiabetic Patients.*

Diabetic Patients		Nondiabetic Patients	
CAUSE OF DEATH	PERCENTAGE	CAUSE OF DEATH	PERCENTAGE
Pulmonary infection	25.6	Pulmonary infection	24.2
Cardiac decompensation	12.3	Carcinoma	14.7
Coronary occlusion	10.8	Cardiac decompensation	12.6
Carcinoma	8.4	Cerebral accident	7.5
Infections, not pulmonary, peritoneal or of extremities	7.7	Infections, not pulmonary, peritoneal or of extremities	5.9
Acute pyelonephritis	7.3	Peritoneal infection	4.8

In an evaluation of the histologic material presented in Table 2, it can be seen that each of the findings is relatively inconstant. Not only were most of the histologic changes haphazard in their occurrence, but all save one were nonspecific from a diagnostic standpoint.

At this laboratory, only glycogen nephrosis or so-called "Armanni–Ebstein cells" in the tubular epithelium of the loops of Henle are considered diagnostic of diabetes mellitus. It is noteworthy that this change was evident to a significant degree in only 42 per cent of the cases. It may be of some interest to note that with the passing years the finding of glycogen nephrosis has become increasingly less frequent, suggesting that adequate therapy may prevent this type of secondary lesion. Intercapillary glomerulosclerosis was present in only 20 per cent of the cases.

Although nuclear changes of the liver cells were the most frequent histologic feature, occurring in 66 per cent of the series, the complete nonspecificity of such changes lends them little significance.

During the eleven years covered by this survey, 45 cases of pigment cirrhosis were autopsied. These cases are not included in the diabetic group inasmuch as the diabetes associated with this disease is considered by all the standard classifications of disease as an entity distinct from diabetes mellitus. Included in the 268 cases studied microscopically, however, were 27 cases with incidental cirrhosis, apparently only coincidental with and in no way specifically related to the diabetes.

It should be re-emphasized that the average age at death of the diabetic patient is almost precisely the same as that of the nondiabetic one. He lives as long today as the latter, but, as brought out by this survey, there are specific hazards that the diabetic patient is more likely to encounter than the nondiabetic, namely, coronary occlusion, peripheral vascular disease, infections of the extremities and acute pyelonephritis.

Summary and Conclusions

An analysis of the causes of death in 307 diabetic patients over the age of twelve, as determined by autopsy findings, is presented.

For purposes of comparison, the autopsies on approximately 2800 consecutive nondiabetic patients were reviewed for anatomic causes of death.

Adequate histologic material available in 268 of the patients in the diabetic group was reviewed to evaluate the frequency of histopathologic changes in diabetes.

From the study, several clinical impressions were confirmed. The diabetic patient lives as long as the

nondiabetic. There are, however, certain hazards that he is seemingly more likely to encounter, namely, coronary occlusion, peripheral vascular disease, infections of the extremities and acute pyelonephritis.

We are indebted to Professor G. Wadsworth, of the Massachusetts Institute of Technology, for statistical analyses of the figures.

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MENINGOCOCCAL MENINGITIS AND MENINGOCOCCEMIA IN CHILDHOOD*

A Statistical Study of Seventy-Two Cases

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MENINGOCOCCAL meningitis, also known as spotted fever or cerebrospinal fever, first accurately described in 1805 by Vieusseux,[1] is always more prevalent during time of war than in peacetime. During World War I, 5839 cases occurring in the armed forces resulted in 2279 deaths, a mortality of 39 per cent.[2] Judging from reports in the recent literature, two facts are apparent: first, that the high incidence of this disease is being repeated, and second, that the use of the sulfonamide drugs has greatly reduced the mortality.[3, 4] Concurrent with the increase of meningococcal meningitis among the military population is an increase among civilians, including children.[5]

During 1943, on the Pediatric Service of the Boston City Hospital, there was a marked increase in the number of children, all under twelve years of age, having meningococcal meningitis or meningococcemia. It seemed that a review of these cases would bring attention to the prevalence of this disease among the younger population and would be valuable to those engaged in the treatment of children with this type of infection.

Etiology

The etiologic agent of this disease is the meningococcus, which was discovered by Weichselbaum in 1887.[6] There are several strains of meningococci that can be demonstrated by immunologic reactions. Gordon and Murray[7] originally described four serologic types, but it is now generally conceded that the majority of pathogenic strains fall into Types 1, 2 and 2*a*. The typing is achieved by mixing the meningococcus with type-specific serum[8] and noting the resulting capsular swelling or agglutination.

The question how the organism enters the body is still a matter of dispute. Some observers have postulated that the meningococcus invades the central nervous system by way of the cribriform plate.[9] The most widely accepted theory, however, is that the bacteria penetrate the mucous membranes of the nose and nasopharynx before entering the blood stream.[10, 11]

Incidence

As shown in Figure 1, the seasonal peak was reached during the spring and late fall, with a drop during the summer. This coincides with the seasonal incidence of upper respiratory infections.

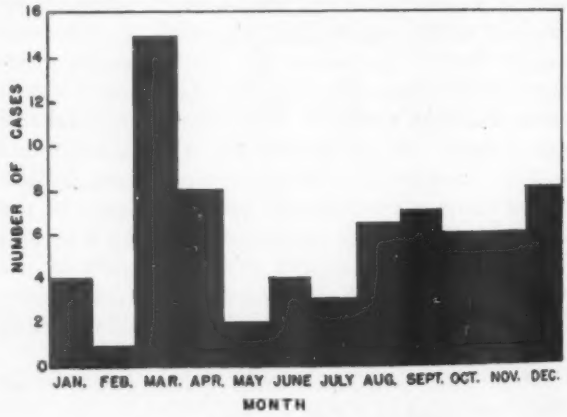

Figure 1. *Monthly Incidence.*

The disease was somewhat more prevalent among girls than among boys, the respective numbers of cases being 40 and 32.

Fourteen cases (19 per cent) occurred in those under one year of age, the youngest patient being nineteen days old, and 41 (56 per cent) in those under five years of age (Fig. 2). This coincides with the report of Holt and McIntosh,[12] who noted a high incidence of the disease in those under five years old.

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Clinical Course

By far the most frequent history was one of sudden onset one day before admission; this was present in 42 cases (59 per cent). In 18 cases the onset occurred two days before admission, in 10 cases three days before admission, and in 2 cases more than four days.

The chief complaint on admission was persistent and often projectile vomiting in 46 cases (64 per cent), headache — either as a principal or a secondary complaint — in 23, stiff neck in 12, a rash in 10, and drowsiness in 10. The other chief complaints were as follows: convulsions (8 cases), fever (7 cases), delirium (7 cases), abdominal pain (4 cases), arthralgia (3 cases), myalgia (2 cases) and coma (2 cases).

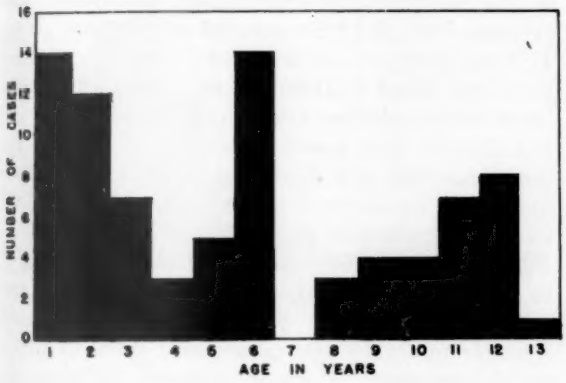

Figure 2. *Age Distribution.*

In 59 cases (82 per cent) a rash was observed on admission. This appeared to be one of the most distinctive features of the disease. The skin eruption was purpuric in nature, resembling the so-called "flea-bite." These petechial hemorrhages occurred very early in the course of the disease, and in many cases multiplied rapidly within a short space of time. They usually appeared on the arms and legs, especially about the ankles. In one case the lesions were maculopapular, resembling the rash present in measles. The diameter of the hemorrhages varied from pinhead size to 3 or 4 cm., the larger ones having necrotic centers. A characteristic of this eruption was the occurrence of the petechial hemorrhages in the mucous membranes of the mouth and eyes, and also on the skin of the palms and soles. This fact was helpful in diagnosing the disease in Negroes, whose skin is lighter on the palms and soles than on the rest of the body, making the eruptions easy to detect.

The cause of this petechial rash is believed to be small, septic, vascular thrombi that form in the small capillaries, causing extravasation of blood into the surrounding tissue.[13, 14] The organisms can be cultured from these spots and can also be directly visualized by the technic outlined by Tompkins.[15] There has been some speculation why the meningococcus has a predilection for the skin and — in the case of the Waterhouse–Friderichsen syndrome — the adrenal glands. Sacks[16] thinks that the meningococcus has an ectodermal tropism that accounts for this. In most cases the hemorrhages faded appreciably within twenty-four hours after treatment and in three days little residual discoloration remained on the skin.

Convulsions were limited almost entirely to patients under three years of age. They occurred in 10 of the 14 one-year-old children, in 4 of the 12 two-year-olds, and in 2 of the 7 three-year-olds. Of the patients over the age of three, only one had a convulsion — a girl of twelve who was treated empirically at home for three days, was admitted in a moribund state and died shortly thereafter.

All the children over one year of age with evidence of meningeal infection had positive meningeal signs, but in most infants no such signs could be elicited. The patients most difficult to evaluate were those less than one year old, apparently because a slight spasm of the muscles is often difficult to detect. A more reliable index is the tension of the anterior fontanelle, which directly reflects the intracranial pressure.

Ten children were drowsy on admission, but only 2 were comatose. Hyperesthesia was present in almost all cases, and in many of them was so severe that the patient objected to any movement of the bed sheets or change in position. Myalgia and arthralgia were frequent complaints on admission. One patient had had such prominent joint symptoms that he was referred to the hospital with a diagnosis of rheumatic fever. Fifty-six patients (77 per cent) were admitted with a temperature of over 102°F.

The Waterhouse–Friderichsen syndrome is characterized by the fulminating onset of a petechial or purpuric skin eruption, a peculiar dyspnea and cyanosis and profound peripheral circulatory collapse.[14] Death usually ensues after a short period of illness. Bilateral adrenal hemorrhage is found at autopsy, and is believed to be the cause of this condition. Nine patients (12 per cent) presented this symptomatology. Of these, 4, one of whom had a meningococcemia, eventually recovered after intensive treatment. Of the 5 patients who died, 2 had meningococcemia. Evidence of adrenal hemorrhage was found in the 3 fatal cases that were autopsied.

In the total series there were 6 deaths, a mortality of 8 per cent. This figure should be qualified, since 5 of these patients were admitted in a moribund state and lived only thirteen hours or less under treatment. As previously mentioned, 5 of the fatal cases showed symptoms similar to those described as the Waterhouse–Friderichsen syndrome. The other patient, although in coma, was neglected at home

for three days before hospitalization and died shortly after admission.

Laboratory Findings

A lumbar puncture was performed on every patient. Ten cases (7 per cent) showed no organisms in the spinal fluid and were therefore classified as meningococcemia without meningitis; six of these patients were under four years of age. Sixty-two patients had a cloudy spinal fluid, with an average count of 6620 cells, 40 to 98 per cent of which were polymorphonuclear (leukocytes).

The sugar content was measured by the rapid method described by Alexander,[17] which has proved extremely reliable and timesaving, being especially valuable at night when ordinary laboratory facilities are unavailable. Absence or diminution of sugar was found in all purulent spinal fluids.

Despite the presence of pus, in 13 cases (29 per cent), the fluid was sterile on culture. Of these cases, 5 exhibited intracellular and extracellular gram-negative diplococci on smear. In the 59 cases in which meningococci were recovered from the spinal fluid or blood, they proved to be Type 1 in 55 (76 per cent) and Type 2*a* in 4 (5 per cent).

The white-cell count on admission averaged 18,050, with a range of 8200 to 39,100. The blood cultures of 24 patients (33 per cent) failed to grow meningococci, although these organisms were isolated from the spinal-fluid culture or visualized on direct smear from the petechiae in most of these cases. The fact that bacteremia exists in the early stage of the disease and is transitory possibly accounts for the many negative blood cultures.[18] No significant anemia directly attributable to the disease could be demonstrated.

Treatment

Prompt and adequate treatment in this disease is imperative and often lifesaving. The entire series of cases was treated with sulfadiazine, orally, subcutaneously or intravenously. In many cases all three methods were employed.

The following outline is a summary of the treatment used in all cases:

A lumbar puncture was done on all suspected cases. If purulent fluid was found, 10 to 20 cc. was removed to reduce the intracranial pressure. This procedure often transformed a disoriented, irritable child into a quiet, sleeping one. The spinal fluid was drained into three sterile tubes, — one for culture, one for a cell count and one for the determination of sugar, chloride and globulin.

Blood for culture and for a white-cell count was taken.

Sodium sulfadiazine was then given by slow intravenous drip in a dosage of 33 to 44 mg. (½ to ¾ gr.) per pound of body weight. In the case of small children, where there is often technical difficulty in administering intravenous therapy, it was found that subcutaneous sodium sulfadiazine was useful. This drug when given in normal saline solution, diluted not to exceed 5 per cent concentration, produces blood levels of 10 to 12 mg. per 100 cc. in half an hour (Jorgensen and Greeley[19]).

Intravenous 5 per cent glucose in normal saline solution was then given to combat the almost universal acidosis and ketosis.

When the blood pressure was low and evidence of the Waterhouse–Friderichsen syndrome was present, 5 cc. of adrenocortical extract was given. This was put into a solution of 15 per cent glucose in normal saline solution and administered by slow intravenous infusion every four hours. The salt and glucose were given to restore the electrolyte imbalance and the depletion of glycogen stores. Synthetic desoxycorticosterone was also given in oily solution intramuscularly.

Sedation was used if the patient continued to be restless. The barbiturates, given either rectally or parenterally, proved to be satisfactory. Lumbar puncture and consequent relief of intracranial pressure, however, seemed to relax the patients enough so that little sedation was needed.

Six hours after the parenteral sulfadiazine had been given, oral sulfadiazine was administered and in most cases was retained without vomiting. This treatment was continued with 10 mg. (1/6 gr.) per pound of body weight every four hours.

If a patient showed evidence of recurrent intracranial pressure by convulsions, persistent vomiting, restlessness or irritability, a lumbar puncture was performed as often as once every four or six hours.

The following day a routine lumbar puncture was done and the spinal fluid was examined for cells, sugar and organisms. It was found that the sugar is the most reliable index of therapy, for if the spinal fluid has been sterilized, the sugar is almost always at a normal or near-normal level.

The urine was closely watched for evidence of sulfadiazine crystals or hematuria. Should these appear, fluids were forced immediately by mouth as well as intravenously, to promote diuresis. Sodium bicarbonate by mouth was also useful in promoting a more alkaline urine. If the urinary findings persisted, however, a shift to the more soluble sulfanilamide was made.

The average duration of chemotherapy was ten days. Sulfadiazine blood levels were determined on alternate days while the drug was being administered. A level of 10 to 12 mg. per 100 cc. was considered adequate.

Following the above treatment, a striking fall in temperature was usually noted. Forty-five pa-

tients were afebrile one week after treatment, and 36 reached a normal temperature and a general feeling of improvement in four days (Fig. 3).

Complications

Arthritis was the most frequent complication encountered, 9 cases (12 per cent) showing evidence of it. This is a somewhat higher incidence than was

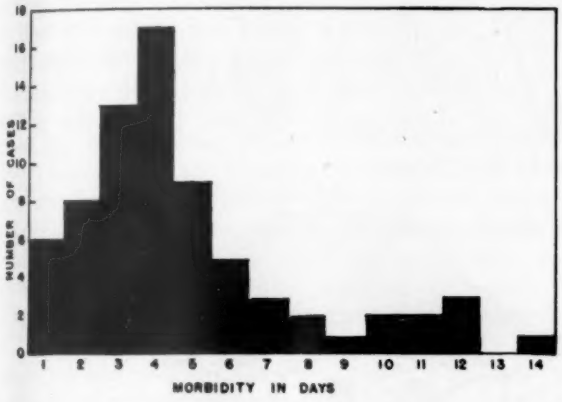

Figure 3. *Morbidity.*

reported in Boulduan's series cited by Schein,[20] in which 13 of 169 patients (7.7 per cent) manifested arthritic signs. The elbow was affected in 7 cases, the knees in 4, and the wrists in 2. Polyarthritis was noted in 4 cases. The average time for the joint manifestations to appear was six days after the onset of the disease. The duration of actual symptoms was eight and a half days. The only treatment required to gain complete function and recovery was immobilization of the involved joint with splints and a flannel bandage. Passive motion and physiotherapy were instituted as soon as it was thought that active inflammation of the joint had subsided. The arthritis appeared to be periarthritic, with thickening and inflammation about the joint but no active suppuration within the joint itself. This is in agreement with the observations of Herrick and Parkhurst.[21]

One case of purulent conjunctivitis, having Type 1 meningococci as the etiologic agent, was observed in a boy of eleven. Boric irrigations and sulfadiazine orally cleared the conjunctivitis, as well as the meningitis, without any complications.

A boy of nine developed complete aphasia one week after hospitalization. This gradually cleared without treatment, leaving no residual signs.

Summary

A series of 72 cases of meningococcal infection in children is presented.

Most cases gave a story of acute onset, ushered in by nausea and vomiting, headache, stiff neck and a skin rash. This rash was a valuable aid in the diagnosis of meningococcemia.

Neurologic symptoms were present in all cases having meningeal involvement. Whereas children under three often had convulsions, older children rarely did.

The predominant type of organism was a Type 1 meningococcus, occurring in 76 per cent of the cases in which cultures were positive.

All cases were treated with sulfadiazine.

The most frequent complication was arthritis, occurring in 12 per cent of the cases. Complete recovery from the arthritis resulted in all cases.

A mortality of 8 per cent occurred, all but 1 of the 6 fatal cases being of the Waterhouse–Friderichsen type. Four children with this syndrome survived.

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SURGICAL MEASURES IN DYSMENORRHEA*

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DYSMENORRHEA, or painful menstruation, is a symptom and not a primary disease. It is referred to as primary when no gross anatomic lesions can be found to account for it, and as secondary when organic disease of the pelvic organs or organs adjacent to them is responsible for the pain. In either case, when the symptom is mild to moderate, relief may be obtained by means of rest, the application of heat to the lower abdomen and the administration of analgesic drugs. Some of the newer antispasmodic drugs, by relaxing the uterine muscle, have proved of benefit, and in a certain group, hormones, notably progesterone, have been of value.

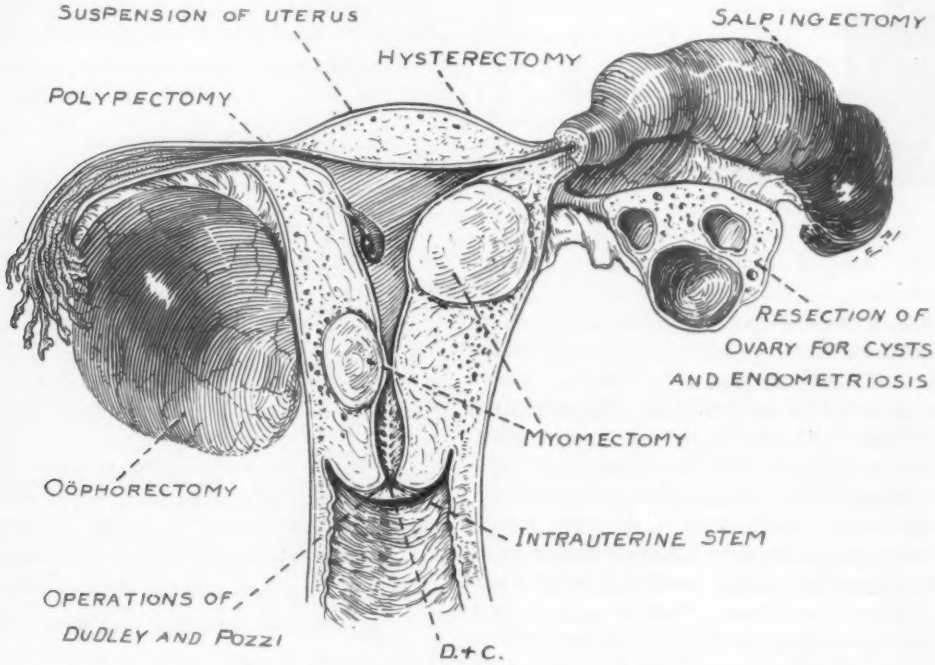

FIGURE 1. *Composite Drawing Showing the Numerous Lesions That Cause Dysmenorrhea and the Various Surgical Measures That Are Employed in Their Treatment.*

In severe cases and in those in which conservative therapy has failed, it frequently becomes necessary to resort to surgical measures. In primary dysmenorrhea thorough dilatation of the cervix, under anesthesia, usually brings relief, sometimes for a number of months and sometimes permanently. This is probably the oldest procedure in use, and years ago it was followed by curettage. Since then, however, it has been determined that it is the dilatation of the cervix rather than the removal of the endometrium that is responsible for the improvement. The use of the intrauterine stem or pessary, which carried considerable vogue a quarter of a century ago, has fortunately been almost entirely abandoned. This instrument, which was sutured to the cervix and left in the uterus for a period of one to three months, did relieve the pain of menstruation in a number of cases, but, as might be expected, it was not infrequently followed by serious pelvic infection, which rarely resulted in death but which caused sterility in a number of the women.

The plastic operations of Dudley and Pozzi, designed to enlarge the external os of the cervix, were based on the theory that the cause of dysmenorrhea is mechanical. An annoying leukorrhea often followed this procedure however, and in many cases gynecologists have had to reconstruct the cervix to as near its original condition as possible in order to overcome this abnormal secretion.

It is in primary dysmenorrhea that presacral neurectomy or resection of the superior hypogastric plexus finds its greatest field of usefulness. The results are frequently dramatic, since it is not uncommon for young women who have been crippled each month by dysmenorrhea to menstruate without discomfort after this therapeusis. Because of the striking results there is the danger of being led

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by one's enthusiasm to perform this operation on those who might be relieved by conservative measures. It should be resorted to only in those cases in which all other methods have failed, and should be reserved for the so-called "spastic" or uterine form of dysmenorrhea, a condition in which the patient experiences severe cramps. It has but little value in dysmenorrhea of ovarian origin.

Secondary dysmenorrhea is pain at the time of menstruation when certain pathologic lesions exist in the generative and adjacent organs. By the surgical ablation of the pathologic process concerned, menstruation may become nearly or entirely painless. Thus, in the presence of myomas that cause pain by the distortion of the uterus and by irregular contractions, in an attempt to expel blood clots, myomectomy or the enucleation of the tumors may result in marked improvement. The excision of endometrial polyps may give similar results, and ablation of the ovaries for ovarian cysts may be responsible for the cessation of menstrual pain.

It is a recognized fact that acquired dysmenorrhea is almost always due to endometriosis of the external variety, in which condition the ovaries are involved in the process. Relief of menstrual pain may be obtained by the resection or ablation of the ovaries, depending on the extent of the disease. Salpingo-oöphorectomy, unilateral or bilateral, may have to be resorted to for endometriosis and for chronic pelvic inflammatory disease in the form of adhesions, hydrosalpinx or chronic pyosalpinx. The last intervention may be performed independently or in association with hysterectomy. In such disorders as uterine myomas and adenomyosis, — also known as internal endometriosis, — hysterectomy, fundic, subtotal or total, with or without the ablation of the adnexa, may have to be employed. In corpus carcinoma the total removal of the uterus and its adnexa is the operation of choice. Since the management of the above-named lesions, which are accompanied by painful menstruation, requires the removal of the uterus or ovaries, or both, thus bringing about the cessation of menstruation, it is obvious that the patient will be relieved of dysmenorrhea.

A number of years ago dysmenorrhea was attributed, in a large measure, to the retroposed uterus and was treated by dilatation and curettage and suspension of the uterus. Uterine suspension nowadays is not so frequently performed as it was in the past. When, however, a retroposition is discovered during a presacral neurectomy, the abdomen being open and the pelvic organs being accessible, the position of the uterus is usually corrected at the same time. The pain occasioned by mechanical disturbances of the vermiform appendix, as found in the retrocecal appendix and the distorted appendix due to adhesions, may be increased at the time of the catamenia. Lysis of the adhesions and an appendectomy frequently help the condition. Similar results may be obtained by attending to the lesions of the ureters, which appear as strictures, calculi and hydroureter. Diseases of the sigmoid and rectum, whether neoplastic, inflammatory or due to endometriosis, which may also cause increased pain at menstruation, demand proper surgical attention, and this secondarily effects improvement in or a cure of the dysmenorrhea. In membranous dysmenorrhea, in which a cast of the endometrium is thrown off with each menstruation, beneficial results have been obtained by curettage and a small dose of radium, about 200 to 250 mg. hr.

Summary

The operative procedures in primary and secondary dysmenorrhea are discussed, and the operative procedures of the contiguous organs, the diseases of which are responsible for pain at the time of menstruation, are considered.

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THE CEREBROSPINAL FLUID PROTEIN IN METASTATIC BRAIN TUMORS

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BOSTON AND CLEVELAND

THE differential diagnosis between a primary and metastatic brain tumor is often difficult, and this study was made to determine whether the protein content of lumbar cerebrospinal fluid is an aid in differentiating these two conditions. All the 43 cases of metastatic brain tumor in this series were verified, either at operation or at post-mortem examination. The fluid was obtained by lumbar puncture before any surgical procedures had been carried out. For comparison, the cerebrospinal-fluid protein of an unselected series of verified primary brain tumors, including astrocytoma, glioblastoma multiforme, meningioma, medulloblastoma and acoustic neuroma, was included in

TABLE 1. *Spinal-Fluid Protein in Cases of Brain Tumor.*

TYPE OF TUMOR	PROTEIN CONTENT (mg./100 cc.)								ALL CASES	
	39 OR LESS		40–99		100–199		200 OR MORE			
	No. of Cases	Percentage	No. of Cases	Percentage	No. of Cases	Percentage	No. of Cases	Percentage	NO.	AVERAGE PROTEIN CONTENT mg./100 cc.
Metastatic tumors	4	9	23	54	12	28	4	9	43	99
Primary tumors:										
Astrocytoma	12	50	8	34	4	16	0		24	55
Glioblastoma multiforme	7	19	19	53	6	17	4	11	36	126
Meningioma	8	26	15	48	7	23	1	3	31	78
Medulloblastoma	3	60	1	20	1	20	0		5	70
Acoustic neuroma	0		1	8	5	38	7	54	13	272

TABLE 2.

CASE NO.	SEX	AGE	PRIMARY TUMOR	LOCATION OF METASTASIS	CEREBROSPINAL-FLUID PROTEIN mg./100 cc.
		yr.			
1	F	43	Carcinoma of lung	Right parietal lobe; subcortical.	27
2	F	49	Medullary carcinoma of breast	Right frontal lobe; superficial. Right and left cerebellar-hemispheres; superficial.	30
3	M	47	Bronchiogenic carcinoma (main-stem bronchus of left lower lobe)	Cerebellar hemispheres, pons, medulla, cerebrum and subependymal lining of both ventricles; superficial and deep.	30
4	F	39	Adenomedullary carcinoma of stomach (cardia)	Right and left frontoparietal lobes and cerebellum; superficial and deep.	30
5	F	65	Carcinoma	Right temporal bone and sphenoid ridge; extradural.	42
6	F	57	Adenocarcinoma	Left parietal lobe; subcortical.	42
7	F	37	Squamous-cell carcinoma of bronchus (left upper lobe)	Left frontoparietal lobe; subcortical.	45
8	F	38	Papillary adenocarcinoma	Left parietal lobe; subcortical.	45
9	F	54	Melanosarcoma	Right temporal and left frontal lobes; multiple superficial nodules.	45
10	F	49	Adenocarcinoma of bronchus (left lung)	Right frontal and temporal; deep. Left cerebellar hemisphere; superficial.	50
11	M	58	Epithelial neoplasm of glandular type (atypical glandlike structures lined by cuboidal or columnar epithelium)	Right cerebellar hemisphere; multiple nodules, deep and superficial.	50
12	M	55	Bronchiogenic carcinoma	Right frontoparietal lobe; superficial.	50
13	F	56	Adenocarcinoma of colon (carcinomatous degeneration of polyp)	Cerebellum	52
14	F	57	Carcinoma	Right frontal lobe.	58
15	M	46	Bronchiogenic carcinoma (left main-stem bronchus)	Left parietal lobe; superficial.	60
16	M	52	Malignant tumor (probably carcinoma)	Right sphenoid ridge	65
17	M	44	Bronchiogenic carcinoma	Left parietal lobe; subcortical.	66
18	M	30	Melanosarcoma (skin of left leg)	Right frontotemporal lobe; deep.	67
19	F	56	Carcinoma of thyroid or hypernephroma	Right parietal lobe; deep.	67
20	M	62	Carcinoma	Left parietal lobe; subcortical.	69
21	M	40	Melanosarcoma (probably skin of right temple)	Right anterior parietal lobe; superficial.	70
22	F	49	Papillary carcinoma of right lung (bronchiolar epithelium)	Right parieto-occipital lobe; deep.	80
23	M	42	Carcinoma of lung	Both hemispheres; multiple small superficial nodules.	85
24	F	53	Carcinoma of breast	Right frontotemporal lobe; superficial.	87
25	M	55	Colloid carcinoma	Right occipital lobe; superficial.	91
26	M	38	Carcinoma	Left parietal lobe; subcortical.	93
27	M	48	Carcinoma of cortex of left adrenal gland	Right parietotemporal lobe; deep.	95
28	F	54	Carcinoma of lung	Right frontoparietal lobe; superficial.	105
29	M	48	Adenocarcinoma	Left frontoparietal lobe; superficial.	108
30	F	46	Papillary carcinoma	Left frontal lobe; superficial.	110
31	F	58	Melanosarcoma	Left frontal lobe; subcortical.	111
32	F	51	Adenocarcinoma	Right parietal lobe; superficial.	111
33	M	58	Carcinoma	Right frontal lobe; subcortical.	126
34	M	34	Melanosarcoma (skin of shoulder)	Left frontal lobe; deep.	130
35	M	50	Bronchiogenic carcinoma (left lung)	Anterior fossa; extradural. Right occipital lobe; superficial.	146
36	F	40	Carcinoma	Right occipital lobe; subcortical.	162
37	M	24	Adenocarcinoma	Right frontal lobe; superficial.	170
38	F	49	Carcinoma of gastrointestinal tract	Left parietal lobe; superficial.	180
39	M	60	Carcinoma	Left frontal lobe; superficial.	186
40	M	34	Epidermoid carcinoma	Right parietal lobe; superficial.	216
41	F	64	Papillary adenocarcinoma	Left temporal lobe; superficial.	242
42	M	63	Adenocarcinoma of lung	Left frontal lobe; superficial.	261
43	F	58	Carcinoma of lung (right upper lobe)	Multiple small lesions disseminated through subarachnoid space; multiple small disseminated lesions. Temporal lobe; large superficial mass.	311

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this study. The distribution of these cases is shown in Table 1.

Merritt and Fremont-Smith[1] included 30 cases of metastatic brain tumor. The cerebrospinal fluid was 44 mg. per 100 cc. or less in 10 cases, 45 to 99 mg. in 15 cases, 100 to 199 mg. in 5 cases, and 200 mg. or more in 2 cases. Hare[2] determined the spinal-fluid protein in 6 cases of metastatic neoplasm. In 2 cases it was normal; in the other 4 it was 66, 77, 125 and 200 mg. per 100 cc., respectively. In Ayer's[3] series, only one metastatic tumor was included, and in this case the protein of the lumbar cerebrospinal fluid was elevated.

The differential diagnosis of glioblastoma multiforme and metastatic neoplasms, which is often confusing owing to the fact that both these tumors develop signs and symptoms rather rapidly, is not helped by determining the spinal-fluid protein. In this series it was normal (40 mg. per 100 cc. or less) in only 19 and 9 per cent, respectively, and the comparative percentages for fluids with varying amounts of increased protein are very close, as shown in Table 1.

Table 2 indicates the separate findings in the 43 cases of metastatic tumor.

It is interesting to note that in 13 of the 26 cases in which the site of the primary lesion was found, it originated from the lungs. This certainly gives support to the rule that all brain tumor suspects should have chest x-ray examination as a routine procedure.

The fact that a neoplasm may be on the surface and even invade the ependyma of the ventricles without causing an elevation of the cerebrospinal-fluid protein is shown in Cases 2, 3 and 4. In all the cases with the greatest elevation of protein, however, the lesions were superficially located in the cerebral hemispheres. Subcortical lesions are also capable of producing a marked elevation of protein, as shown in Cases 31, 33, 34 and 36. In the metastatic tumors, there was no apparent correlation between the type of primary tumor and the degree of elevation of protein.

The tendency of metastatic lesions to invade the supratentorial areas is brought out in this study, since there were only 6 patients with subtentorial metastatic neoplasms. Also, the protein was not markedly elevated in any of these, the highest level being 52 mg. per 100 cc. Hare[2] has found that primary subtentorial tumors, exclusive of acoustic neuromas, do not cause so great an increase in cerebrospinal fluid protein as do the supratentorial lesions. This is also apparently true of metastatic tumors.

Summary

The average protein content of lumbar cerebrospinal fluid in 43 cases of metastatic brain tumors was 99 mg. per 100 cc.

Ninety-one per cent of the cases had a protein content greater than 40 mg.

The highest protein content was found in the cases with superficial cerebral metastases.

The patients with supratentorial metastases had a higher protein content than did those with subtentorial lesions.

The protein content of lumbar cerebrospinal fluid alone does not differentiate a metastatic neoplasm from a primary brain tumor.

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MEDICAL PROGRESS

TUBERCULOSIS

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TUBERCULOSIS is a disease of innumerable ramifications; its many branches reach out from medicine and the allied sciences into the distant realms of sociology and law. Significant as all these ordinarily are, in time of war the main interest is in its great military importance.

TUBERCULOSIS, WAR AND POSTWAR

Tuberculous Rejectees

Last year special emphasis was placed on the ways and means that had been designed to keep tuberculosis out of the armed services.[1] Now, after three years of war, attention is shifting from case finding in inductees to the proper handling of tuberculous rejectees and veterans.

Although the follow-up of men rejected for tuberculosis varies in some details throughout the country, the general principles followed are fundamentally alike everywhere. Registrants disqualified for military service because of tuberculosis become, to a great extent, the responsibility of public-health officials, and their cases are submitted for study and review by competent authorities. Such follow-up is necessary since the degree of activity of a chest lesion cannot be determined from a single x-ray film. In fact, a definite diagnosis of tuberculosis cannot be made from a single roentgenogram. Hence, follow-up enables one to sort out the tuberculous from the nontuberculous, and the active from the inactive or arrested. The programs adopted by Chicago[2, 3] Wayne County, Michigan,[4] and Massachusetts[5] have recently been discussed.

In Chicago, the Medical Advisory Board in conjunction with the Municipal Tuberculosis Sanitarium determines the disposition of cases rejected for tuberculosis. Of 1907 men with pulmonary tuberculosis seen in Chicago, 1279 were finally classified as 4*F* and 628 as 1*A*. Of the total number, 1431 cases (75.4 per cent) had never been previously reported to the Board of Health — a striking demonstration of the value of this type of case finding. On further study by the Collapse Therapy Clinic, 429 were selected as prospective candidates for treatment, and of these, 59 are now receiving pneumothorax.

In Massachusetts, rejectees for pulmonary diseases are first reported to the State Department of Public Health, and are subsequently referred to local boards of health for further clinical and laboratory study. Practically all the rejectees are eventually examined in clinics conducted by the city, county or state. Of 2270 men so studied, 1795 (79.0 per cent) were rejected for pulmonary tuberculosis, 1672 of them with the reinfection type of disease. Complete follow-up was obtained in 1125 cases, and the diagnosis of reinfection-type disease was confirmed in every case. Of 395 men rejected as "pulmonary suspects," 160 received further study, and of these 86 were found to have tuberculosis. Important, though less striking than the Chicago demonstration, was the fact that two thirds of the cases of pulmonary tuberculosis that were discovered had never been reported to boards of health. Besides, 60 per cent of the cases were believed to be in need of immediate hospitalization. Thus, follow-up returns some men to the Army and sends others to sanatoriums or clinics for therapy.

Tuberculous Veterans

In spite of the many safeguards that have been set up to keep tuberculosis out of the armed services, it is disconcerting to learn that, up to the present, discharges from the Army because of this disease number approximately 10,000.[6] Freer[7] has estimated that 35 of every 10,000 men accepted for service have minimal, scarred or arrested lesions, and attributes some of the mistakes that have been made to inexperience, haste and fatigue of the examiners.

Myers,[8] in a critical review, further analyzes the reasons for the failure to detect all cases of tuberculosis on induction into military service. Listed among the salient points are omission of x-ray examination of about 1,000,000 men who were first inducted, the use of the 4-by-5 inch or 35-mm. film instead of the 14-by-17-inch film, and the fact that even the best films cannot detect every case of tuberculosis. Myers stresses the role that could have been played by tuberculin testing of inductees and laments its exclusion from routine induction examinations. His original paper deserves careful reading.

There is, nevertheless, some reason to believe that the number of discharges for tuberculosis will soon show a progressive decline, and the figures from the Navy[9] and from the Army Air Center at Nashville[10] lend encouragement to this viewpoint. Men examined for air-crew training at this center are between eighteen and twenty-six years of age,

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and all have been in the Army for varying periods up to two and a half years. Examination of this group by the photoroentgen method revealed that the percentage incidence of tuberculosis in the first 32,000 was 0.207 per cent, in the second 32,000 0.169 per cent, and in the third only 0.120 per cent. In the last 10,000 examinations, indeed, it was less than 0.050 per cent. It is of some interest, too, that of the active cases of tuberculosis discovered, 112 were in the minimal stage, 10 were moderately advanced, and only 2 were advanced.

The Veterans' Administration is making every effort to absorb the load of new cases of tuberculous victims who have been discharged from military service. Statistics computed as of January 31, 1944, disclose that a total of 6114 beds were available for tuberculous veterans.[11] Under the so-called "G. I. Bill of Rights," plans were developed to provide an additional 3500 beds,[12] and this project has already received presidential approval.[13]

Unfortunately, tuberculosis among veterans is but little controlled by the availability of hospital beds or the expenditure of huge sums of money. Dublin[14] points out that financial arrangements to veterans are such as to have had "the unfortunate effect of providing an incentive to many men to discontinue hospital treatment and to attempt a cure at home." In spite of the many millions of dollars that are being spent, the experience of veterans' hospitals has been unfavorable. For example, in 1942 less than 2 per cent of the patients were discharged as arrested. Hospitalization was considered incomplete in more than half the cases.

The reason for this alleged "deplorable situation," according to Dublin,[14] is that veterans come and go as they please. Some have had as many as twenty-four different admissions; six to eight admissions is a commonplace occurrence. Yet the consequences of this indifference to treatment are far reaching. "The discharge of men," says this author, "before they are cured has left its toll on the entire country." Obviously, laws pertaining to veterans' benefits must be modified if tuberculosis among them is to be controlled.

The attitude of World War II veterans toward tuberculosis can arouse nothing but pessimism. Wolford[15] reports that of 2275 such veterans treated for active pulmonary tuberculosis, approximately 31 per cent had left against medical advice before treatment was completed. Dublin[14] writes, "There is already evidence that all is not well with the new tuberculosis victims, and that they are showing the same restlessness, the same abandonment of hospital care." An understanding of the dangers and seriousness of tuberculosis appears to be sadly lacking in too many servicemen. Altogether too often the term "tuberculosis" is regarded as being synonymous with a "short, pleasant vacation in the mountains."

United States Public Health Service

The establishment of a Division of Tuberculosis Control in the United States Public Health Service on July 6, 1944, may be "one of the most important steps yet taken toward the ultimate control of this disease."[16] For this reason Section 2 of the bill[17] under which this division was founded is quoted in detail.

> *Section 2.* To enable the Surgeon General of the Public Health Service (1) to make studies, investigations, and demonstrations with respect to developing more effective measures of prevention, treatment and control of tuberculosis; (2) to assist through state health authorities, by grants as otherwise provided in this act, states, counties, health districts, and other political subdivisions of states in establishing and maintaining adequate measures for the prevention, treatment, and control of tuberculosis, including construction, maintenance, and operation, and the training of personnel for state and local health work; (3) to control the spread of tuberculosis in interstate traffic; and (4) to meet the cost of pay allowances, and traveling expenses of commissioned officers and other personnel of the Public Health Service detailed to assist in carrying out the purposes of this act, and for administration of this act, there is hereby authorized to be appropriated for the fiscal year ending June 30, 1945, a sum of $10,000,000 and for each fiscal year thereafter a sum sufficient to carry out the purposes of this act.

In several articles, Hilleboe[16, 18, 19] has elaborated on the purposes of the Division of Tuberculosis and has reviewed some of its accomplishments. The objectives of an adequate control program, he insists, must include mass x-ray examination (eventually, of the entire population), follow-up of discovered cases, isolation of open cases, treatment for active cases, periodic check-up, health education, research and financial aid to the afflicted. For the first step — mass roentgenography — the Public Health Service has available ten transportable units, some of which are equipped with the new photoelectric timer — a device that simplifies x-ray procedure by eliminating the necessity for measuring each subject's chest.

Industrial areas and large cities are the chief targets of the United States Public Health Service at the present time. Of 778,496 war workers examined by photofluorography up to May 31, 1944, approximately 1.0 per cent were found to have tuberculosis, and in two thirds of these cases the disease was in the minimal stage. Hiebert[20] reports a survey of 21,427 persons conducted in Kansas with a unit borrowed from the United States Public Health Service. Attention was centered on persons in war industries and "critical areas," and definite reinfection tuberculosis was found in 0.5 per cent. These figures are comparable to those of Massachusetts, where an x-ray survey of 28,190 persons in thirty-nine industrial companies revealed 352 cases of pulmonary tuberculosis, 114 of which were probably active.[21]

Hospital Personnel

It is common knowledge that medical students, nurses and others who assist in the care of tuberculous patients are exposed to a definite risk of

infection. Schultz[22] cites the cases of 24 medical students, 8 of whom developed active disease. He presents evidence that this group was carelessly exposed, and goes on to suggest that medical school faculties include in their curriculums definite programs to teach students the technic of handling patients with infectious diseases and that facilities for such precautions be provided. Certainly it is as important for students to learn how to protect themselves against tuberculosis as it is to detect it.

A recent survey by the Royal College of Physicians[23] is also instructive for the hints it provides for controlling tuberculosis among nurses. Mantoux tests and x-ray examinations were performed on 3764 nurses shortly after their entry into training school. Study of tuberculosis morbidity in those whose x-ray films were clear on entry revealed that 33 cases had occurred in 452 nurses initially Mantoux negative, but only 43 cases in 2120 initially positive. The annual case rate was 7.4 per 1000 for Mantoux-positive nurses, in contrast to 18.8 per 1000 for Mantoux-negative ones. It is therefore apparent that the young nurse who is tuberculin negative must be given special care and that her exposure to tuberculosis should be kept at a minimum.

Childress[24] reviews his experience with 5039 employees at the Grasslands Hospital, a general hospital of 800 beds, 300 of which are for tuberculous patients. If these employees are divided into two approximately equal groups, exposed and unexposed, it is found that 39 (1.8 per cent) of the exposed and 6 (0.2 per cent) of the unexposed developed tuberculosis. All these 45 employees originally had negative x-ray films and were symptom free. In this study, the laboratory was found to be a serious source of danger, since 5 active cases were discovered in the laboratory, in addition to several cases in physicians who worked there. There is no doubt that in many instances protection to laboratory workers against tuberculosis is wholly inadequate.

Foreign Countries

Throughout the world intensified programs for the control of tuberculosis are already under way or plans for the future are being laid. Mass photofluorographic check-up in Saskatchewan, Canada, has proved to be such a practical success that it has been stated that no city or municipality is so small or so large that it cannot raise the cost of such a survey.[25] In Alaska, where less than 100 beds are available for 2500 tuberculosis cases, proposals are being considered for the construction of hospitals to provide at least 400 more beds.[26] In Rio de Janeiro,[27] where tuberculosis is the leading cause of death, with an estimated death rate for 1944 of 309 per 100,000 population, and in other South American countries,[28] mobile x-ray units are being used and hospital facilities are being extended. Reports from Victoria, Australia, indicate an increasing death rate from tuberculosis, and a program has now been launched that includes provision for 2000 beds and roentgenologic examination of every child at the age of twelve.[29] In fact, postwar plans have been made for compulsory chest x-ray examination of every person.[30]

Trends and Perspectives

The tuberculosis mortality in the United States for the years 1939–1941 has been statistically analyzed by Yerushalmy and his co-workers.[31] The death rate continues to show a gratifying decline: in 1942 it was 43.1 per 100,000 population, whereas in 1943 it was only 41.9. In highly industrial areas, however, especially in the north-central and northeastern states, an increase has been noted.[32]

A series of articles has appeared on the important problem of the apparently adequately treated patient whose sputum is occasionally positive or contains rare bacilli. Stokes[33] points out, "It cannot be denied that many patients with only a few bacilli in the sputum can and do lead comfortable, useful and economically productive lives and do not infect other members of their households." He recommends that discharge of patients from sanatoriums be not solely determined by the status of the sputum, but that consideration be given to such factors as age, sex, resistance, economic status and occupation.

In a more recent review, the Pottengers[34] call attention to the fact that tubercle bacilli may be detected on rare occasions in so-called "converted cases" if tests are done often enough and an exacting technic of examination is used. They believe that not every patient with an infection of the lung with rare bacilli in his sputum is necessarily suffering from active disease. In their studies, there has not been a single case in which a contact exposed to these patients has developed progressive clinical tuberculosis. Before discharge, a patient must indicate from every aspect that his lesion is healed; the sputum is but one item in the over-all picture.

Willis,[35] in a general discussion, has wisely summed up the problem as follows: "It is the duty of the laboratory to find tubercle bacilli wherever it can and to report them when found; the duty of the clinician is to evaluate the situation." The presence of tubercle bacilli may establish the diagnosis, but its significance may be totally different where therapy, discharge, prognosis and epidemiological connotations are concerned. Willis believes that there is a growing attitude of reasonableness about discharging patients for whom all has been done that can be done and who still occasionally produce a few bacilli.

Chemotherapy

During the past year, self-styled "science writers" have surpassed themselves in beguiling the public with a fleeting succession of hopes for a quick and

dramatic cure for tuberculosis. Often by innuendo, less frequently by misstatement, preliminary in vitro or guinea-pig experiments have been presented as clinical successes. Usually these alleged "cures" depend on the discovery of a new "wonder" chemical or so-called "protective" vaccine. Chemicals and vaccines are being developed, but progress in this direction is slower and less certain than the laity is led to believe.

The chemical compounds of greatest promise are the sulfones. The parent drug, 4,4′–diaminodiphenylsulfone, is a potent agent for combating tuberculosis in guinea pigs,[36] but its toxicity limits its clinical application. Derivatives are therefore being synthesized in an attempt to obtain more suitable compounds for therapeutic use. The two derivatives that have received the greatest amount of study are promin (sodium *p,p′*–diaminodiphenylsulfone–*N*, *N′*– didextrose sulfonate) and diasone (disodium formaldehyde sulfoxylate,4,4′-diaminodiphenylsulfone).

Three reports emphasize the value of promin in experimental tuberculosis in guinea pigs. In one group of tests, a favorable therapeutic effect in these animals was noted even though treatment was delayed for six weeks and the promin was given only in alternate weeks.[37] In another series of experiments, the average survival time of the treated animals was twice as long as that of untreated guinea pigs.[38] If the guinea pigs were first vaccinated, the subsequent administration of promin caused an even greater inhibition in the progress of the disease than occurred in the nonvaccinated animals.[39]

Clinically, promin is not considered to be a particularly potent curative agent against human tuberculosis.[40] At the Wisconsin State Sanatorium, 27 patients with poor prognosis were given from 0.4 to 1.2 gm. of promin daily by mouth for a nineteen-month period. The status of 16 patients was ultimately evaluated; the improvement noted was greater than would otherwise have been expected. In another group of 36 adequately treated patients, marked improvement was observed in 7 and moderate improvement in 5.[41] The authors of this report conclude, "Prolonged administration of promin orally is clinically feasible . . . [and makes] more extensive and more exactly controlled observations highly desirable." They stress the point that human beings, unlike guinea pigs, have a high degree of natural resistance to tuberculosis and are usually in need of but little aid in order to turn a losing fight against this disease into victory. When the fight is against tuberculous meningitis, however, promin has proved to be without any beneficial result in either prolonging or maintaining life or altering the course of the disease.[42]

The clinical use of diasone has been discussed in some detail by Petter,[43–45] who fed the compound to 100 volunteers and analyzed the results of treatment in 44 of them. Diasone, it was concluded, is not an ideal chemotherapeutic agent but is to be regarded as a useful adjunct to other treatments. No correlation was discovered between the blood level of diasone and the clinical course. Toxic reactions were not infrequent but were not marked or irreversible. On the other hand, one very severe dermatitis was reported in another series of 63 cases.[46] Jellinek[47] found no useful effect from diasone in 15 cases of extrapulmonary tuberculosis.

A significant addition to the growing list of chemotherapeutic agents is promizole (4,2′–diaminodiphenyl–5′–thiazolesulfone).[48, 49] It is apparently the least toxic of the therapeutic chemicals and is comparable in its effectiveness for guinea pigs to promin and diasone. Experimentally it is administered in daily doses of 200 to 250 mg., and favorable effects can be noted even in guinea pigs that have been inoculated ten to fourteen weeks earlier. Because of its low toxicity, it has been given orally to 56 patients in daily doses of 10 to 16 gm., but insufficient time has elapsed for evaluation of the results. A two-year-old child who presumably had tuberculous meningitis was treated with promizole and recovered,[50] but the diagnosis was not established with bacteriologic certainty and the result of a tuberculin test was not reported.

Among other compounds that have been tested for their bacteriostatic or bactericidal action on tubercle bacilli are certain naphthoquinones[51] and stilbestrol.[52] The latter exhibits a surprisingly strong bactericidal action in vitro. Penicillin and penicillium extracts have, by and large, no effect,[53] but another mold, as yet unidentified, is reported as having a bacteriostatic action.[54]

Practically all the workers in this field of chemotherapy recognize the difficulties that are encountered in evaluating any agent for therapeutic use in human beings. The need for large numbers of cases, carefully matched controls, bacteriologic proof of disease and the objective, impartial evaluation of its course is stressed by Hinshaw and Feldman.[55] Pinner,[56] on the other hand, believes that absolute-control experiments in human beings are an impossible attainment and that any therapeutic agent, to be satisfactory, must be decisive in its results or is doomed to eventual discard.

Surgery

Lloyd[57, 58] has initiated a one-man campaign that is destined eventually to put pneumonology on a broader, sounder basis. Two features of this campaign are especially noteworthy. The first — inclusion of a chest service in a greater number of general hospitals — is designed to bring treatment for tuberculosis closer to the many persons who cannot obtain this service conveniently at present. The second feature — a bronchoscope for every lung specialist — is a natural outgrowth of the increased

use of bronchoscopy for the diagnosis and treatment of lung diseases.

Endobronchial Tuberculosis

McConkey and Gordon[59] have stressed the fact that tuberculous stenosis of major bronchi can be diagnosed clinically with an accuracy approaching 100 per cent. The cardinal symptom is wheezing. The diagnostic sign is the presence of rhonchi, occasionally audible, more frequently palpable, usually in expiration, and loudest over the stenotic bronchi. In their series of 95 tuberculous patients there were 61 who during the course of their disease developed persistent sonorous rhonchi unrelieved by cough. In 58 (95 per cent), the diagnosis of bronchial stenosis was confirmed bronchoscopically.

Lloyd and Budetti[57] have presented a comprehensive account of bronchial tuberculosis based on their experience with 475 bronchoscopic examinations. From the etiologic standpoint, they believe that tuberculosis in the parenchyma of the lung is always accompanied by changes in the mucous membrane of the draining bronchus. From the therapeutic standpoint, they find that although in some cases bronchial ulcerations heal spontaneously, cauterization is never of any value. Bronchial disease interferes more or less with drainage from the parenchymal focus, and this interference may be aggravated by collapse measures, especially pneumothorax. Hence, it is important to ascertain the state of the bronchi before attempting any collapse therapy.

A recent paper by Stone[60] gives an excellent description of the clinical aspects of endobronchial tuberculosis. In addition to wheezing and rhonchi, the author points out that the presence of an opaque or unexpandable lung during the course of pneumothorax is strongly suggestive of an underlying bronchial stenosis. Pain or soreness in the sternal region is described as a symptom in 30 per cent of the cases. Other diagnostic hints that are indicative of bronchial disease include failure of a cavity to close by thoracoplasty and clinical evidence of tuberculous bronchiectasis.

It must be remembered, however, that not all bronchial stenosis is due to tuberculosis. A fairly definite syndrome, benign nontuberculous bronchial stenosis, has been described.[61]

Major Surgery

Much of the recent literature on lobectomy and pneumonectomy for tuberculosis has already been reviewed by Blalock[62] and Strieder.[63] Both these surgeons wisely caution that the use of resection for pulmonary tuberculosis is still in a formative stage and urge that the indications be not too rapidly extended. Time, rather than large series of cases, is necessary before the role of resection can be properly evaluated.

On the basis of their vast experience with lobectomy and pneumonectomy, Overholt and Wilson[64] have reached the following tentative conclusions: the operations are not associated with any unusual technical problems; tuberculous bronchitis or a positive pleural fluid is not necessarily a contraindication, nor is activity in the resected lung or stable (arrested) disease in the contralateral lung. Of sixty-three resections performed by Overholt from 1934 to 1943, thirty-five were pneumonectomies and twenty-eight lobectomies. The chief indication for operation was the presence of multilobar, predominantly unilateral disease. In forty-five consecutive resections since January, 1942, only 2 patients had contralateral spread; 2 had empyema, but none had a persistent fistula. In this group there were 36 reasonable-risk patients, and the operative mortality among them was 5.7 per cent. Conversion of sputum, however, was obtained in less than 70 per cent of the patients.

The ideal method for treating large cavities that remain open in spite of intensive collapse measures has not yet been found, but the progress made in this direction by Vineberg and Kunstler[65] is encouraging. They describe a method for needling such cavities and obtaining direct manometric readings of the intracavitary pressure, and they recommend that this procedure be carried out on cavities larger than 2.5 cm. before any major measure for surgical collapse is attempted. Special instruments are used for this test, and precautions are taken against complications such as empyema. On the basis of pressure determinations, Vineberg and Kunstler find that tuberculous cavities fall into three categories: those with an open bronchus and atmospheric pressure, those with a closed bronchus and negative pressure and those with check-valve mechanism and positive pressure. The last group, that of "tension cavities," has always presented a most difficult therapeutic problem, for such cavities are but little affected by surgical collapse. Negative-pressure giant cavities, on the other hand, close readily with thoracoplasty. The writers point out that it is the indiscriminate use of intracavitary drainage that has brought this valuable method of treatment into disrepute. Transthoracic intracavitary suction drainage should be employed only when a tension cavity is present, since this is the only true indication for its use. By the judicious application of suction, such cavities are reduced to the size of a catheter and can then be readily closed by thoracoplasty. The authors have performed needling of cavities in 150 cases and suction drainage in 27, without a single complication of hemorrhage, empyema, spontaneous pneumothorax or air embolism. Their valuable paper should be read by all who attempt any major chest surgery.

Almost supplementary to the methods described by Vineberg and Kunstler[65] is the technic outlined

by Judd[66] for closing residual cavities following thoracoplasty. By an operative maneuver that he calls "lung mobilization and fixation," there is created a positive and forceful pressure on the cavity, and even some tension cavities can be closed by this method. With as trying a surgical problem as the tension cavity, it is good to have more than one method of approach.

A paper by Medlar and his associates[67] should prove of some aid in the surgical handling of chest diseases, since it provides for more accurate roentgenologic localization of lesions in relation to the pulmonary lobes. By employing an ingeniously constructed artificial thorax, they have obtained satisfactory roentgenograms of the interlobar septums in a variety of different positionings. They have thus devised a scheme in which the fourth and sixth costovertebral junctions serve as landmarks and by which the lobar distribution of the pulmonary disease can be readily recognized roentgenologically.

Vitamins

The complex relation of vitamins to tuberculosis has many components, but there are two aspects that must not be confused with each other and must be discussed independently. The first is largely a problem in biochemistry, since it concerns the detection and the measurement of extent of vitamin deficiencies in tuberculous patients. The second is entirely a therapeutic problem, since it deals with the administration of vitamins for the correction of nutritional deficiencies and for the treatment of tuberculosis or its complications. To phrase the problem somewhat differently: Do vitamin deficiencies occur in tuberculosis, and if so how much can be gained by vitamin therapy? Unfortunately, a survey of the literature yields only incomplete answers to both questions at the present time.

The unqualified statement can be made that multiple vitamin deficiencies do occur in some tuberculous patients. This point has been established with reasonable certainty in spite of the facts that so-called "normal" vitamin levels are often established arbitrarily[68–70] and that assays of a given patient's diet may be untrustworthy.[71]

Getz and his co-workers[68–70] have discovered vitamin A deficiencies both by dark-adaptation tests and by blood-level estimations and, as might be expected, the deficiency of vitamin A is roughly proportional to the extent of tuberculous involvement. Breese and his associates[72] fed measured amounts of vitamin A to 29 tuberculous patients, estimated its blood levels at given intervals thereafter, and found that in normal controls the rise of vitamin A in the blood was twice that of tuberculous patients. While admitting wide variations in single cases, the authors infer that in tuberculosis vitamin A is poorly absorbed from the intestinal tract and suggest that in this disease the diet be above average for vitamin A. An opinion has also been expressed that tuberculous diabetic patients are in special need of this vitamin, and a daily dosage of between 150,000 and 200,000 units has been recommended.[73]

Tuberculous persons may also be deficient in vitamin C.[69, 70, 74] From studies on Navajo Indians, Pijoan[71, 74] has concluded that tuberculous patients require an intake of vitamin C at least twice as great as that of normal persons to maintain a fixed plasma level of 0.7 mg. ascorbic acid per 100 cc. Pijoan[74] states, "This does not mean that vitamin C is to be specifically used in the treatment of tuberculosis as a therapeutic agent but rather as an adjunct to maintain proper ascorbic metabolism compatible with effective body economy." This confirms earlier work in which 24 patients were given 100 to 200 mg. of ascorbic acid daily, and in which it was found to be of no value in the treatment either of tuberculosis or of its complications, such as hemoptysis.[75]

Nutritional studies by Farber and Miller[76–78] disclose that deficiency in niacin, thiamine and vitamin K may also occur. According to these authors, hypoprothrombinemia was found to exist in 33 per cent of nonbleeding and 53 per cent of bleeding patients. The prothrombin time could be restored to normal in the majority of cases by the parenteral administration of menadione, but in spite of restoration to normal, hemoptyses often continued. Massive hemorrhages, in fact, sometimes occurred in patients with a normal bleeding time. The authors believe that it has not been established that vitamin K stops pulmonary hemorrhages or influences the course of the disease. In small hemoptyses, as Levy[79] points out, vitamin K may help to control bleeding, but evaluation of therapy for hemoptysis is a most difficult and uncertain task.

The relation of the B complex of vitamins to tuberculosis is but poorly understood. Extremely ill patients with far-advanced tuberculosis have a multitude of clinically detectable nutritional deficiencies, and some of these, it is true, are due to avitaminosis. In these extremely sick and often moribund patients, tuberculosis behaves more like a malignant process than an infectious disease, and efforts to stem the wasting of the body almost invariably end in failure.

According to Farber and Miller,[77, 78] more than 75 per cent of acutely ill patients show some evidence of avitaminosis B. For treatment they recommend a basic supplement of 90 gm. of brewer's yeast, 150 mg. of niacin, and 6 mg. of riboflavin in divided daily doses. In specific deficiency states, up to 600 mg. of niacin, 15 mg. of riboflavin and 50 mg. of thiamine may be given daily. The authors noted some improvement in approximately 85 per cent of the patients so treated, but whether this therapeutic regime has any effect on the outcome of the tuberculosis is not stated. My own experience[80] with thiamine as a stimulant of appetite in tuberculous

children has been disappointing. As for riboflavin, decision concerning its significance must be withheld at present, since there is evidence that in some circumstances it may not be a dietary essential.[81]

During the last few years, McConkey[82] has urged that cod-liver oil and tomato juice be employed in the treatment and prophylaxis of intestinal tuberculosis. From his assembled statistics it is inferred that the decline in the occurrence of this complication was coincident with the increased sale of cod-liver oil and canned citrus juices and the increased use of these preparations in his sanatorium. Be this as it may, the role of vitamin D in tuberculosis is still obscure, and accurate knowledge of its behavior is almost entirely lacking. A brief but excellent discussion of the therapeutic use of vitamin D in tuberculosis has appeared,[83] and it should be read before a course of vitamin D therapy is planned for the patient.

Miscellaneous Topics

Bacteriologic technic and problems. Rapid methods have been described for concentrating and staining sputum specimens for tubercle bacilli. Reliable concentrations can be obtained by using a 5.25 per cent solution of sodium hypochlorite (Clorox) as a digestant.[84, 85] Staining of specimens can be performed effectively at room temperature by adding propylene glycol to the staining mixture.[86] These technics should prove valuable timesavers for those laboratories already harassed by the lack of trained technicians.

The exact status of fluorescence microscopy for the detection of tubercle bacilli is still under discussion. The physical principles that underlie the method should be understood by those who attempt to use it. Laboratory studies show that it is roughly on a par with the Ziehl–Neelsen method for sputum examinations, but on gastric concentrates twice as many positive cases can be detected.[87] According to Graham,[88] fluorescence microscopy will not be ready for general use until it has been evaluated under the most favorable conditions that can be afforded by the average laboratory.

Variation in the virulence of tubercle bacilli is a problem that often plagues those working in the fields of bacteriology or immunology. Label designations may be unreliable. An approximate index of the degree of virulence can be rapidly obtained by injecting a measured suspension of weighed bacilli into the ear vein of a guinea pig.[89] Other experiments indicate that in vitro measurements of virulence can be obtained by culturing acid-fast bacilli with graduated amounts of diphtheria antitoxin.[90, 91] Whether diphtheria antitoxin has any therapeutic role is not known, but some laboratory and clinical research is being conducted that may provide an answer to this question.[92]

Virulence can apparently be altered by the presence of other micro-organisms as well as by chemicals. Streptococci inoculated into rabbits seem to enhance the virulence of tubercle bacilli simultaneously or previously injected.[93] Avirulent human tubercle bacilli, on the other hand, have a definite retarding action on the course of the disease when injected into guinea pigs together with virulent bacilli.[94]

Ultraviolet irradiation. Lurie[95] has demonstrated that in known strains of rabbits ultraviolet irradiation reduces the incidence of air-borne tuberculosis. In one set of experiments, 11 of 15 animals (73 per cent) exposed to air-borne tuberculosis in a non-irradiated room developed tuberculosis, and the disease was fatal in 9 cases, whereas not a single rabbit in the irradiated room became ill. Rabbits of low resistance as well as those of high resistance are protected by high-intensity irradiation.

Pregnancy. From a study of 26 women with advanced tuberculosis who received collapse therapy before giving birth to one or more children, Cutler[96] concludes that if the diseased area is anatomically well collapsed, the patient is afforded considerable protection against spread of the disease. Conversely, in cases in which an unsuccessful collapse is obtained, the prognosis is poor.

Congenital heart disease. When congenital heart disease complicates tuberculosis, pneumothorax is often delayed for fear of placing too heavy a burden on the cardiovascular system. That this idea is erroneous is borne out by the studies of Auerbach and Stemmerman,[97] who studied 13 such patients, 7 of whom came to autopsy and 5 of whom had pneumothorax. They state: "In view of . . . the fact that our own patients succumbed to the pulmonary involvement rather than to failure of the defective cardiovascular system, active treatment of tuberculosis is recommended. Pneumothorax induced in 5 of our patients did not lead to congestive failure in any instance."

Pneumothorax and airplane travel. By and large, persons with pneumothorax (artificial or traumatic) should be cautioned against traveling by airplane. Two well-planned articles, one published in this country[98] and the other in England,[99] point out that the moderate altitudes (5000 to 12,000 feet), usually attained by commercial airplanes are sufficient to produce a pronounced increase in the size or pressure of a pneumothorax. The risk of air travel is especially great in the presence of recently active disease, adhesions or reduced vital capacity and shortly after refills. If a patient with artificial pneumothorax must undertake a flight, he should go just before a refill, not immediately after one. An altitude of 4000 feet is regarded as the uppermost limit of safety for traumatic pneumothorax cases.

Diagnosis of early tuberculosis. In the diagnosis of early tuberculosis, even the best roentgenograms may be deceptive, since the disease actually begins as a microscopic lesion and interpretation of the

x-ray film is based on the gross appearance. Medlar and his associates[100, 101] have presented remarkable demonstrations of this fact from both the clinical and experimental standpoints. By exhaustive laboratory studies, these authors were able to demonstrate tubercle bacilli in 2 per cent of a group of patients whose x-ray films were regarded as negative. In a subsequent series of experiments with rabbits who were intravenously inoculated with bovine tubercle bacilli, lesions were produced that could be carefully controlled and studied. Among the many important conclusions derived from this research was the fact that for a lesion to give a shadow, an area at least the size of a primary lobule must be densely packed with disease.

Vaccination with the vole bacillus. First isolated in 1937, the vole bacillus is a slow-growing Mycobacterium, apparently a third type of fixed mammalian tubercle bacillus." It is highly pathogenic for the vole, causes localized lesions in other laboratory animals, is innocuous to fowls, and gives no evidence that it will produce progressive disease when inoculated into man. In the experiments described by Brooke and Day,[102] viable vole bacilli, heat-killed vole bacilli and Calmette-Guérin bacilli were compared in their effectiveness for protecting guinea pigs against subsequently induced experimental human tuberculosis. The results demonstrate that under the conditions established in these experiments, viable vole bacilli are at least equal, and probably superior, to Calmette-Guérin bacilli in their immunizing properties.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30521

PRESENTATION OF CASE

A sixty-two-year-old fireman was admitted to the hospital in collapse.

Two days prior to admission the patient visited the Out Patient Department because of dysuria and frequency. Rectal examination in the Urological Clinic showed a moderately enlarged, smooth, firm, nontender prostate, and catheterization revealed a residual of 330 cc. in the bladder. Because the procedure was rather traumatic, he was admitted to the Emergency Ward for two days, the stay being uneventful. Immediately following discharge, while stooping to tie his shoes, he began to sweat profusely and complained of severe precordial pain. While climbing some stairs immediately afterward he again broke out into a cold sweat, emitted a queer noise from his throat, which sounded to his wife like a "death rattle," and, on reaching the street, vomited and collapsed. He was immediately admitted to the hospital.

The patient had been a known hypertensive for about five years, and had been complaining of dyspnea on climbing stairs, fatigability and slight ankle edema. He had taken digitalis off and on for two years. Seven months prior to admission he had visited the Nerve Clinic because of an attack of headache, vertigo, vomiting and memory loss lasting about two days and followed by a dull ache about the right ear, which was relieved by aspirin. At that time the blood pressure was 175 systolic, 100 diastolic. The heart was enlarged, with an accentuated aortic second sound, and an occasional premature beat was noted. Many moist rales were present at the lung bases. There was a constant tremor of the head and arms, which was said to have increased over a period of ten years.

The family history revealed that one brother had heart disease and another was confined in a mental institution. His mother had died at fifty-three of a "shock."

Physical examination revealed a dyspneic, deeply cyanotic man. There was an incessant tremor of the hands and head. Respirations were Cheyne-Stokes in type. Bilateral arcus senilis and retinal arteriosclerosis were present. There were sticky rales at the lung bases. The heart was enlarged, the left border being 2 cm. outside the midclavicular line. Auscultation revealed slow fibrillation, with the pulmonic second sound greater than the aortic; no murmurs were heard.

*On leave of absence.

The temperature was 97.6°F., the pulse 76, and the respirations 20. The blood pressure was 110 systolic, 90(?) diastolic.

Examination of the blood revealed a red-cell count of 6,100,000, with 13 gm. of hemoglobin and a hematocrit of 62. The white-cell count was 15,600, with 82 per cent neutrophils. The urine had a specific gravity of 1.016 and a 0 to +++ test for albumin; the sediment contained 10 red cells, many white cells and rare hyaline and granular casts per high-power field. The serum nonprotein nitrogen was 110 mg. per 100 cc., and the van den Bergh test was 0.5 mg. direct, and 1.2 mg. indirect.

On the night of admission the patient was restless and vomited several times. He was given oxygen, together with 0.19 gm. of quinidine sulfate every four hours, 0.1 gm. of digitalis a day, 0.25 gm. of sulfathiazole three times daily and paraldehyde for sedation. The following morning he vomited clear fluid containing a small amount of bright-red material. The pulse rate was 110, and he was sweating.

A portable roentgenogram of the chest revealed a hazy increase in density in the right chest that had a ground-glass appearance and was most marked at the right base. The left lung did not show this haziness. The heart was greatly enlarged in the region of the left ventricle. Examination three days later revealed marked increase in the pulmonary process (Fig. 1). The right lung was particularly dull, with numerous areas of increased density through which only little aerated lung could be seen. The hilar shadows and blood vessels were enlarged, and there was increased marking throughout the left lung without the diffuse haziness seen on the right.

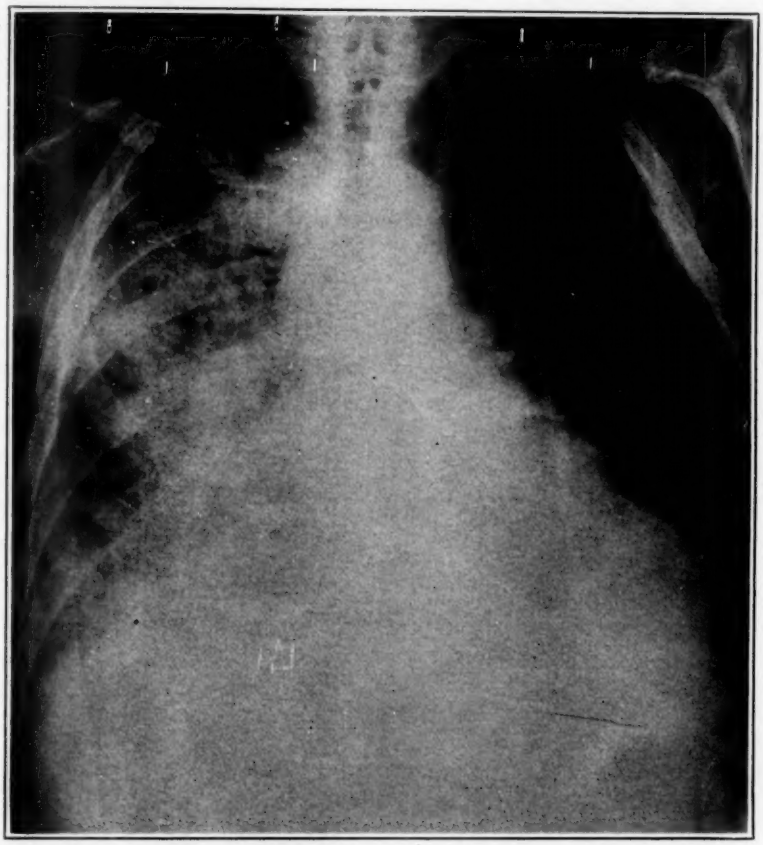

FIGURE 1. *Roentgenogram of Chest.*

Four electrocardiograms were taken (Fig. 2), the first one on the day of admission, the second one two days later, the third one two days after that, and the last one two weeks after the third. All four electrocardiograms showed auricular fibrillation. The first one (Fig. 2*A*) showed, in addition, a run of regularly occurring ventricular complexes at a rate of 160 in Lead CF_5 with wide QRS waves; this almost certainly indicated ventricular paroxysmal tachycardia but was not shown at any other time. The first electrocardiogram also showed small, but definite, Q waves in Lead 1 that were of unusual shape and distinctly abnormal, along with elevated ST segments in Leads 1 and CF_4, in the latter the

elevation being extremely high. R waves were absent in Lead CF_4. There was slight late inversion of the T waves in Leads 1 and CF_5. There were also two ectopic ventricular contractions in other leads on this first occasion. The second electrocardiogram (Fig. 2*B*), taken two days later, showed a distinct change except for the auricular fibrillation. The small Q waves in Lead 1 persisted, but there were almost no R waves in that lead, and small S waves had appeared. The T waves were slightly inverted. In Leads 2 and 3 there were distinct and striking changes: deep Q waves had appeared, the ST segments had become a little elevated, and the T waves were inverted. In the precordial leads the ST segments were within normal limits. In the third electrocardiogram (Fig. 2*C*), two days after that, there was an abrupt shift in the limb leads back toward the first record, in that there was no longer any Q wave in Lead 3, and Q wave in Lead 2 had become much smaller, and there was a deep wide Q wave in Lead 1. The T waves were flat to low in the three limb leads. There were no R waves in Leads CF_4 and CF_5, and the ST segments were elevated in both these leads, with low T waves. In the last record, taken two weeks after the third, the record in general resembled the previous one.

Because of the possibility that a pulmonary infarction had occurred, a bilateral superficial femoral-vein ligation was performed on the second hospital day. The patient's lips remained cyanotic, and the neck veins moderately distended. On the third hospital day he complained of a "stitch" in the left chest anteriorly, just medial to the nipple, on coughing or on deep breathing. He gradually improved on a cardiac regimen augmented with oxygen. The serum nonprotein nitrogen gradually fell to normal, but the patient continued to have orthopnea, some dyspnea and moderate cyanosis. He showed a gradually increasing degree of confusion, with marked memory defect and lack of time orientation and insight.

On the twenty-sixth hospital day oxygen was

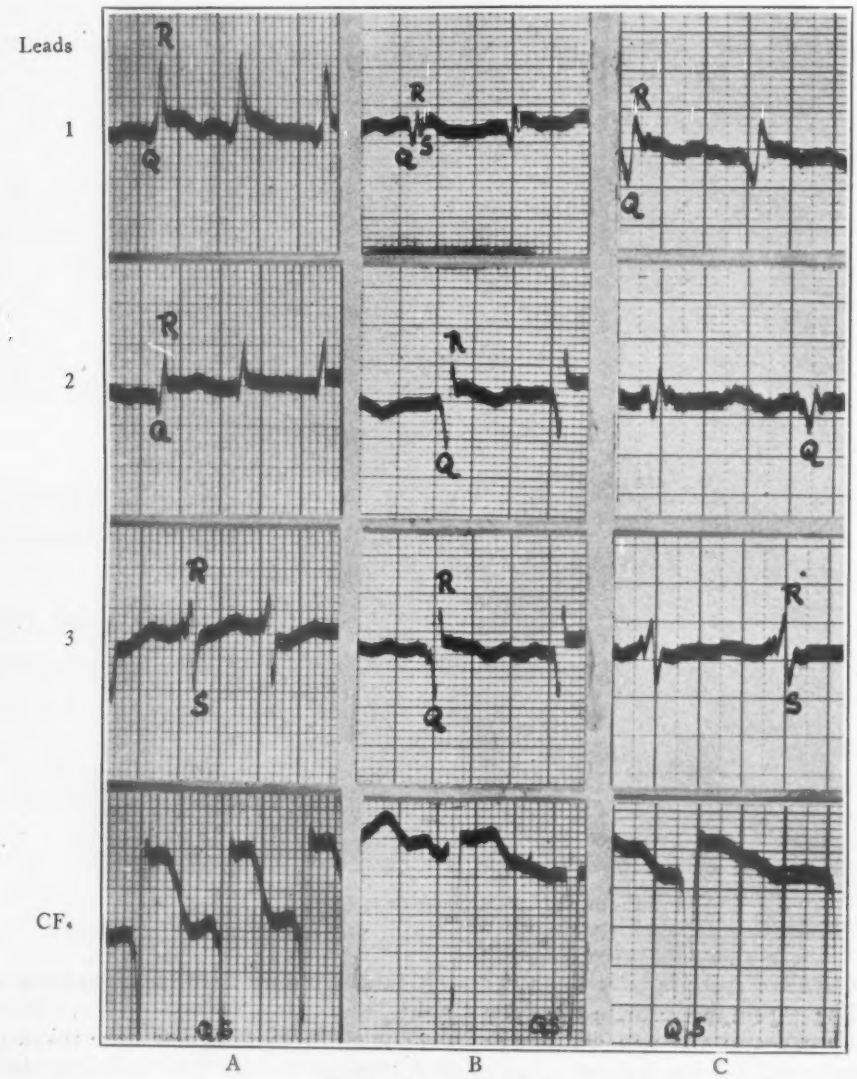

FIGURE 2. *Electrocardiograms.*

A *was taken on the day of admission;* B, *on the third hospital day; and* C, *on the fifth hospital day.*

discontinued, since it did not appear to affect his status appreciably. He continued to fibrillate, and the lungs became almost clear to auscultation. The serum nonprotein nitrogen rose to 105 mg. per 100 cc., and the white-cell count, which had fallen to 9400, rose to 19,400. On the thirty-fifth hospital day he had a brief attack of shock, during which the blood pressure was unobtainable for a short period. He became increasingly confused, cyanotic and dyspneic and expired on the fortieth hospital day.

Differential Diagnosis

Dr. Maurice Fremont-Smith: This patient was a sixty-two-year-old man with a family history of vascular disease who manifestly had hypertensive heart disease with failure and probably some coronary disease. On the other hand he came to the hospital because of urinary symptoms and was catheterized, 330 cc. of urine having been removed from the bladder. The prostate was not thought to be large by rectal examination. One cannot tell much about urinary obstruction by rectal examination; this patient manifestly had obstruction, and long-continued obstruction can cause elevation of the nonprotein nitrogen. He left the hospital after catheterization, had some sort of an acute episode with precordial pain and then collapsed.

I believe that any one of five things could have happened to him. He might have had a coronary thrombosis, and that is perhaps the first choice. He could have had a rupture of a dissecting aneurysm, since he was a known hypertensive. Against this is the fact that the pain was anterior rather than posterior. In dissecting aneurysm pain occurs chiefly in the back between the shoulder blades or lower. In coronary thrombosis there may be pain in the back between the shoulder blades, but if present it is always associated with greater pain anteriorly. He could have had a cerebral accident, which might have caused the state of shock but could not have accounted for the precordial pain. He could have had simply a change in cardiac rhythm. Sometimes that causes precordial pain, and in a man with a poor heart, such a change in rhythm, the onset of fibrillation, for instance, may cause collapse. He could have had a pulmonary infarct, since the circulation was poor. Of course I am influenced by the fact that they tied the femoral veins; someone must have thought that he had a pulmonary infarct. The cerebral accident, with headache, vertigo, vomiting and memory loss, I cannot explain except on the basis of small cerebral thromboses, which are part of the general picture of a bad vascular situation.

The systolic blood pressure was 175, but I am quite sure that it had been higher because he was already in failure. After he came into the hospital it was 110 systolic, 90 diastolic, and he was manifestly in shock. He had a red-cell count of 6,000,000 and a hematocrit of 52, which indicate either concentration from dehydration or, likelier, a chronic compensatory erythremia from anoxemia, the result of heart failure. The white-cell count of 16,000 may have been due to concentration or possibly to a response to a pulmonary infarct. The urine is interesting because at one time he had no albumin and because the nonprotein nitrogen came down to normal in the hospital; both these findings argue against an actual uremia in the sense of primary kidney disease. He may have had back pressure from the prostate, which would interfere with the function of the kidneys. He certainly could have had a rising nonprotein nitrogen with myocardial infarction, owing to insufficient circulation to the kidneys. The van den Bergh test was slightly elevated, probably as a result of chronic passive congestion of the liver. He was restless and vomited several times on admission. He was given oxygen, which is reasonable, quinidine sulfate to protect him against ventricular fibrillation, which is reasonable, and digitalis.

I want to say a word about the sulfathiazole. They gave it cautiously in exceedingly small doses, probably for the urinary infection. It may have been given because the patient was on constant drainage. I should like to know about that.

Dr. Jacob Lerman: Yes; that is correct.

Dr. Fremont-Smith: One should be particularly careful in giving sulfonamides to elderly people with bad kidneys, remembering that one may get toxic symptoms, particularly anuria, with very small amounts of sulfonamides. In any case the main thing to remember is not to give treatment that may do harm. I am interested in an article on the toxic symptoms of sulfonamides by Vilter and Blankenhorn,[1] especially the discussion by Dr. David Lehr, who has carried out animal experimentation. Dr. Lehr states that if they give plenty of alkali, animals survive very large doses of sulfadiazine; they do not get into difficulty with the kidneys, and when they are killed, no pathologic changes are found. If, on the other hand, animals that have an obstruction in the pelvis or have developed crystals are given alkali, they die rapidly. If given plain water, they die from water intoxication. Under these conditions the tubules reabsorb all the fluid and no water gets into the collecting tubules. The medication that brought about the greatest benefit in cases with a deposit of crystals were salts, either sodium chloride or a mixture of sodium bicarbonate and ammonium chloride. Apparently, if one gives a large amount of electrolytes, reabsorption from the tubules does not take place and fluids are excreted through the kidney, thus washing out the sulfadiazine crystals; but plain water or sodium bicarbonate given at the time of obstruction is detrimental. If one is going to protect a patient against sulfonamide crystalluria, apparently one should

start the alkali before starting the sulfonamide; if the alkali is started later, it is not so valuable.

I shall say a word or two about paraldehyde. Paraldehyde is looked on as a safe drug, but Burstein[2] has reported 2 fatal cases, and by animal experimentation he found that with toxic doses animals die of right auricular dilatation. The difference between the effective dose and the toxic dose with paraldehyde is extremely slight. In psychotic patients with a good heart, paraldehyde seems to be a safe drug, but in a person with cardiac failure one should possibly think twice before giving a drug that produces fatal cardiac dilatation in animals.

Why did this patient vomit red material? Patients with chronic nephritis develop acute ulcer, and so do those with uremia. He may have had an ulcer, but it may have merely been evidence of chronic passive congestion in an old man who was vomiting.

I think that we might see the x-ray films at this time.

Dr. Laurence L. Robbins: There is obvious enlargement of the heart, even though the film was not taken for the heart size, and a rather diffuse increased density throughout the medial portion of the right lung with some involvement at the base. In the first film there is nothing characteristic about the appearance. The second film (Fig. 1) shows a more diffuse process. The bronchi remain open, and the greater portion of the process appears to be within the lung. Certainly there is some fluid in the right pleural cavity, and a small amount in the left. One thing about it is that all the shadows appear to be more sharply defined than they were at the time of the previous examination.

Dr. Fremont-Smith: Would you say that the findings are consistent with pulmonary infarcts?

Dr. Robbins: If it is an infarct, it is a massive affair, and I should have to place the embolus in the main pulmonary artery.

Dr. Fremont-Smith: Do you think that it is a diffuse bronchopneumonia?

Dr. Robbins: I do not know. It does not look characteristic of anything. It could be consolidation throughout the lung, with bronchopneumonia as a terminal affair, but this film was taken some time before he died. So far as I am concerned it could be a massive infarct or a diffuse pneumonia, with a small amount of pleural effusion on each side.

Dr. Fremont-Smith: That is certainly consistent with the diagnosis of pulmonary infarct.

Dr. Robbins: If it is an infarct, it is the largest one that I have seen.

Dr. Fremont-Smith: An infarct of that size should have been immediately fatal. I wish that Dr. White would discuss the electrocardiograms, which are beyond my depth. I should like to know whether the electrocardiograms differentiate pulmonary infarct and coronary disease. I should say that this patient had coronary disease, whether recent or old I do not know.

Dr. Paul D. White: The electrocardiograms are extremely interesting. One of the most significant findings is not the auricular fibrillation but the other disturbance of rhythm found on the first day, namely, the probable ventricular paroxysmal tachycardia, which strongly suggests myocardial infarction or the toxic effect of digitalis. Furthermore, the variations in the QRS waves, ST segments and T waves in the limb and precordial leads are also particularly significant and confusing. The first (Fig. 2*A*), third (Fig. 2*C*) and fourth electrocardiograms are absolutely characteristic of the effect of anterior myocardial infarction, as shown by the Q waves in Lead 1, the absence of the R waves in Leads CF_4 and CF_5 and the ST segment elevations in Leads 1, CF_4 and CF_5. We might have expected, however, more definite inversion eventually of the T waves in Leads 1, CF_4 and CF_5, which did not develop during the time in which these electrocardiograms were taken.

The second electrocardiogram (Fig. 2*B*), taken two days after admission, is the one that is the most interesting because of the abrupt temporary but striking differences from the first and the later electrocardiograms. Here the findings suggest those either of posterior myocardial infarction or of an acute cor pulmonale superimposed on some effects of the anterior myocardial infarction. The deep Q waves, the inversion of the T waves in Leads 2 and 3 and the small S waves in Lead 1 make one think of a cor pulmonale. The effect is, in the main, temporary, and the T waves in Leads 1, CF_4 and CF_5 may have failed to become inverted in later records, owing to the increased pulmonary pressure. Thus, the electrocardiograms show a complicated condition either in the form of multiple involved myocardial areas or in the form of a combination of the factors of myocardial infarction and of acute cor pulmonale.

Dr. Fremont-Smith: I think that this patient had hypertensive and coronary heart disease, with cardiac infarction and probably pulmonary infarction, obstructing prostate and urinary infection. There may have been a terminal bronchopneumonia as well; and there was, of course, generalized arteriosclerosis and cerebral arteriosclerosis.

Dr. Lerman: I should like to make a few comments in answer to some of the questions raised by Dr. Fremont-Smith. The mental state was probably due to anoxemia. The patient was always cyanotic and markedly orthopneic. I can visualize him tossing around in bed in a disoriented manner. The bizarre nitrogen fluctuations undoubtedly were due to the fact that he pulled out his catheter every so often. Whenever he did that, he became obstructed and the nitrogen values rose. I do not know the exact interpretation of the unusual x-ray changes, but as I recall it the explanation was that they were

caused by an infarct and pulmonary edema. He certainly would have died immediately if the extensive lesion had been solely due to an infarct. Consequently we thought that the picture was partly caused by edema.

Clinical Diagnoses

Cardiac failure, with coronary heart disease.
Hypertension.
Pulmonary infarct.
Uremia.

Dr. Fremont-Smith's Diagnoses

Hypertensive and coronary heart disease, with cardiac infarction.
Obstructing prostate (? uremia), with urinary infection.
Generalized and cerebral arteriosclerosis.
Pulmonary infarct.

Anatomical Diagnoses

Coronary thrombosis, recent: left descending branch.
Myocardial infarct, recent: anterior wall.
Mural thrombus: left ventricle.
Thrombus occluding right pulmonary veins: left atrium.
Hemorrhage, severe: right lung.
Alveolar fibrosis: right lung.
Hydrothorax, bilateral.
Pericardial adhesion.
Chronic passive congestion with central necrosis of liver.
Nephrosclerosis, mild.
Renal infarcts.
Prostatic hypertrophy.
Urinary bladder hypertrophy, with trabeculation and pseudo diverticulums.
Arteriosclerosis, severe, generalized.
Operation: femoral vein ligation, bilateral.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy showed an unusual condition. There was a thrombus of the descending branch of the left coronary that had produced a massive myocardial infarct in the anterior wall of the left ventricle, over which was a large mural thrombus (Fig. 3). In the left auricle was a ball-shaped thrombus, 3 cm. in diameter, which was well organized and only slightly adherent to the auricular endocardium but which could easily be pulled away leaving a not too ragged endocardial lining. This thrombus had completely plugged the openings of both right pulmonary veins, so that little blood was coming from the right lung. There was no extension of the thrombus into the veins. The openings of the left pulmonary veins were normal. The entire right lung was dark, hemorrhagic and firm and weighed over 1000 gm., whereas the left lung was crepitant and weighed slightly under 400 gm. Certainly not much blood, if any, was coming from the right lung, which accounts for the marked contrast between the roentgenologic appearance of the right and the left lung. It is

Figure 3. *Photograph of Heart.*

intriguing to speculate how the occluding thrombus originated. There was a small and much more recent mural thrombus in the left auricular appendage that may have been the source. The occluding thrombus looked much like the mural thrombus over the ventricular infarct, but it would be rather farfetched to assume that a piece of it traveled against the current through the mitral valve into the auricle. It may have been produced merely by the auricular fibrillation.

Dr. White: Did the auricular myocardium look all right?

Dr. Castleman: Yes; there was no infarction. We have to assume that the thrombus was there at the time of admission to the hospital because the change in the right lung was seen in the first film. Although the lungs in gross suggested infarction there were no emboli or microscopic evidence of infarction. The left lung showed slight chronic passive congestion. At first glance it looked like infarction, but all the alveolar walls were intact,

and the alveoli were filled with blood. The other striking thing in the right lung and not in the left was the presence of numerous areas of fibrosis within the alveoli (Fig. 4), a picture that Masson[3] has described in rheumatic pneumonia. It occurred to me that perhaps these fibrous plugs should not be ascribed to rheumatic pneumonia but to pulmonary hypertension, since they were not present in the other lung. We know that most rheumatic patients have mitral stenosis with pulmonary hypertension, and perhaps we have here a clue to the cause of so-called "Masson bodies." There were no hyaline membranes of the alveoli, another finding in some cases of rheumatic pneumonia.

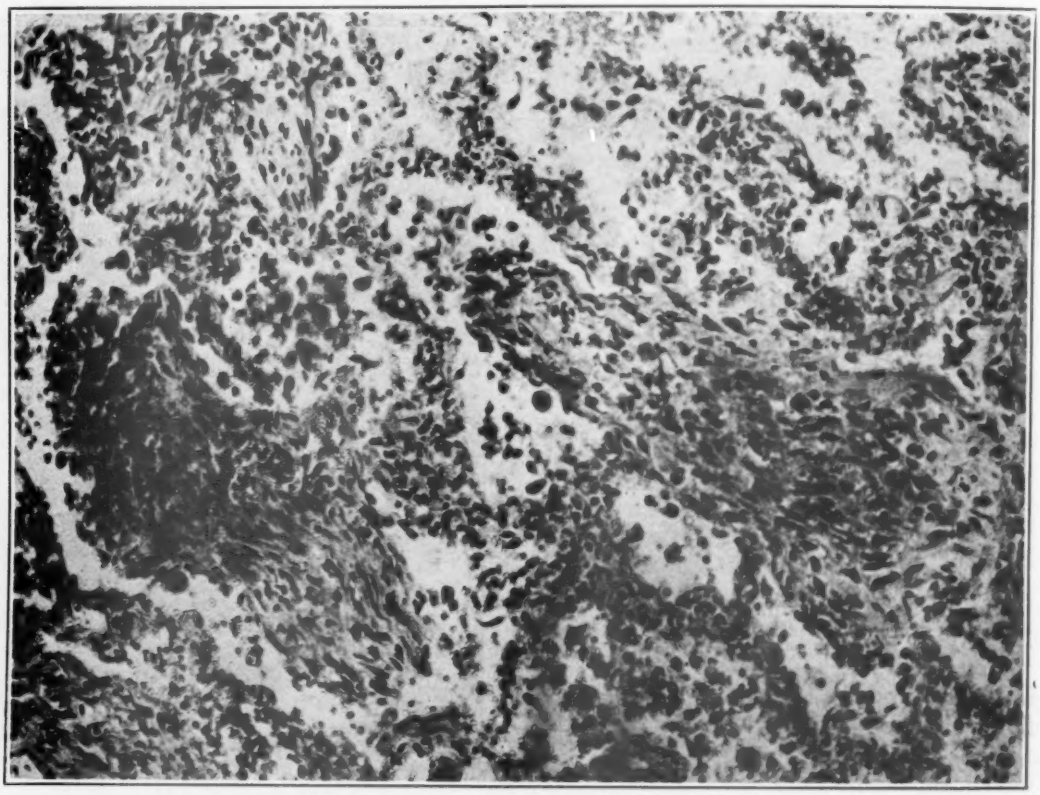

FIGURE 4. *Photomicrograph of Lung Showing Intra-Alveolar Fibrosis.*

DR. WHITE: Do you know of a similar case in the literature? I have never heard of one.

DR. CASTLEMAN: No.

Another finding was a hypertrophic and trabeculated bladder due to prostatic enlargement, with no evidence of distention of the renal pelves or pyelonephritis. There were a few renal infarcts, which must have been produced by emboli from the mural thrombus in the heart. There were also thrombi in the deep veins in the legs, but none of these could have reached the lungs because of the bilateral femoral-vein ligation.

DR. WHITE: I should like to make a further comment about the electrocardiograms. We hesitate to state that any electrocardiographic findings are pathognomonic, but we can almost surely say that prominent Q waves in Lead 1, especially when carried over to Lead 2, are rarely found in any condition other than anterior myocardial infarction. If Lead 1 is upside down, owing to congenital dextrocardia, that is another thing.

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CASE 30522

PRESENTATION OF CASE

A twenty-year-old married woman was admitted to the hospital with persistent diarrhea.

The patient was perfectly well until a year prior to admission, when she had an attack of "intestinal grippe," with abdominal pain, malaise and cough, which was productive of phlegm but not of blood. After a few days she again felt well. About two months later she first noted some red streaking at stool and had a mild diarrhea. A local physician was consulted, and she was treated for hemorrhoids, without effect. The diarrhea and bleeding became

progressively worse and were associated with weakness, anorexia and loss of weight. About nine months prior to entry, in spite of her increasing symptoms, the patient was married. Following marriage, she appeared to improve somewhat but soon developed a cold, associated with an exacerbation of her symptoms. She had lost 18 pounds since the beginning of her illness, dropping from 116 to 98 pounds, and because of increasing weakness she entered a community hospital. The red-cell count was said to have been 2,600,000. After five weeks of symptomatic treatment, augmented by transfusions, she was discharged considerably improved, the red-cell count having risen to 4,300,000. She was sent to a convalescent home, where she gained weight and strength. The diarrhea had practically ceased and there was no blood in the stools. One month later, about five and a half months before admission, she developed a sharp, stabbing pain in the right upper thorax just below the shoulder, made worse by respiration. The pain lasted about a week and was treated by diathermy. Shortly thereafter she developed severe bloody diarrhea and was again hospitalized. A sigmoidoscopic examination at that time was said to reveal "pinpoint ulcers that bled easily." She suffered severe abdominal pain, requiring morphine for relief. Four months before entry she was transferred to another hospital, at which time she was bleeding profusely by rectum and appeared almost in extremis. She complained of cough, which was accompanied by a small amount of white frothy sputum and chest pain, and was running a low-grade, undulating fever without chills. There was no hemoptysis. A roentgenogram of the chest revealed elevation of the right half of the diaphragm and increased density over the entire right lung; the latter was interpreted as being due to pleural effusion, but several taps were unsuccessful. The left chest was clear. A loop ileostomy was performed, and a spontaneous ileostomy developed proximal to the operative ileostomy two weeks later. In spite of the ileostomy, numerous transfusions and nearly 1,000,000 units of penicillin, the patient showed no improvement and had several major hemorrhages by rectum. About one and a half weeks before entry she had a sudden attack of dyspnea and cyanosis, with a temperature of 105°F., apparently following an injection of penicillin. The next day the temperature was 95°F., and she subsequently improved rapidly.

The patient was born in Oklahoma and had lived there until shortly before the onset of her illness. She had had three attacks of rheumatic fever at the ages of seven, nine and seventeen years, respectively, without apparent sequelae.

Physical examination revealed an extremely weak, lethargic, markedly cachectic woman. The skin was cold, dry and pale, with little subcutaneous fat. The skin around the ileostomy openings was inflamed, undermined and tender. The scars of several decubitus ulcers were present. There was an infected area over the sternum, apparently the site of a bone-marrow infusion. The chest was small and sunken, with marked splinting on the right. The lower half of the right chest was dull to percussion anteriorly and posteriorly, and breath sounds over this area were diminished to absent. Elsewhere on the right the breath sounds were bronchovesicular with numerous coarse inspiratory rales. The left chest was clear. There was a rough apical systolic murmur obliterating the first sound. There were flexion contractures of both legs and slight clubbing of the fingers.

The temperature was 100°F., the pulse 90, and the respirations 25. The blood pressure was 80 systolic, 40 diastolic.

Examination of the blood revealed a red-cell count of 4,000,000, with 55 per cent hemoglobin, and a white-cell count of 9000, with 70 per cent neutrophils and 30 per cent lymphocytes. The urine was essentially negative. The blood serum nonprotein nitrogen was 21 mg. per 100 cc., the protein 4.9 gm., with an albumin-globulin ratio of 1.4, and the chloride 89–99 milliequiv. per liter. The van den Bergh test was 1.1 mg. per 100 cc. direct, and 1.8 mg. indirect. The prothrombin time was 38 seconds (normal, 18 to 20 seconds). A tuberculin test in a dilution of 1:1,000,000 was negative.

A roentgenogram of the chest (Fig. 1) revealed a miliary process scattered throughout both lung fields, with dense consolidation in the middle lobe on the right and evidence of some consolidation in the right lower lobe. The right half of the diaphragm was not clearly visualized. There appeared to be a cavity in the posteroinferior portion of the right lower lobe that was connected with a bronchus. The heart and mediastinum appeared to be in normal position, and the liver and spleen were enlarged.

The patient was given transfusions, infusions and penicillin. On the second hospital day she developed sudden dyspnea and cyanosis, with distended neck veins and many inspiratory rales and wheezes. The pulse was 120, and the respirations 35. Following the use of tourniquets, oxygen and Cedilanid she improved rapidly. The following day examination revealed moderate edema of the lower extremities. There was no engorgement of the neck veins. The point of maximum cardiac impulse was felt 2 cm. beyond the midclavicular line. The heart rhythm was regular, with a diastolic gallop. The second pulmonic sound was extremely loud, and there was a questionable mid-diastolic rumble at the apex. An electrocardiogram showed rather low T waves but nothing of definite diagnostic value. The patient continued to run a fever between 100 and 103°F. A spasm of coughing on one occasion was productive of a small amount of bloody sputum that was negative on smear for acid-fast organisms. She had several attacks of pulmonary edema similar

to the first, all of which responded promptly to therapy. A proctoscopy revealed a rough bleeding mucosa with many pseudopolyps. Another roentgenogram of the chest on the ninth hospital day (Fig. 2) revealed a marked change, the right lung appearing completely consolidated. Several bronchi in the right lung were seen to contain air, and the miliary process in the left lung had somewhat increased. X-ray examination of the abdomen revealed no evidence of dilated loops; there was enlargement of the spleen, but no definite enlargement of the liver. Examination of the fundi showed venous stasis and slight papilledema but no tubercles or infarcts.

On the thirteenth hospital day, the patient expired.

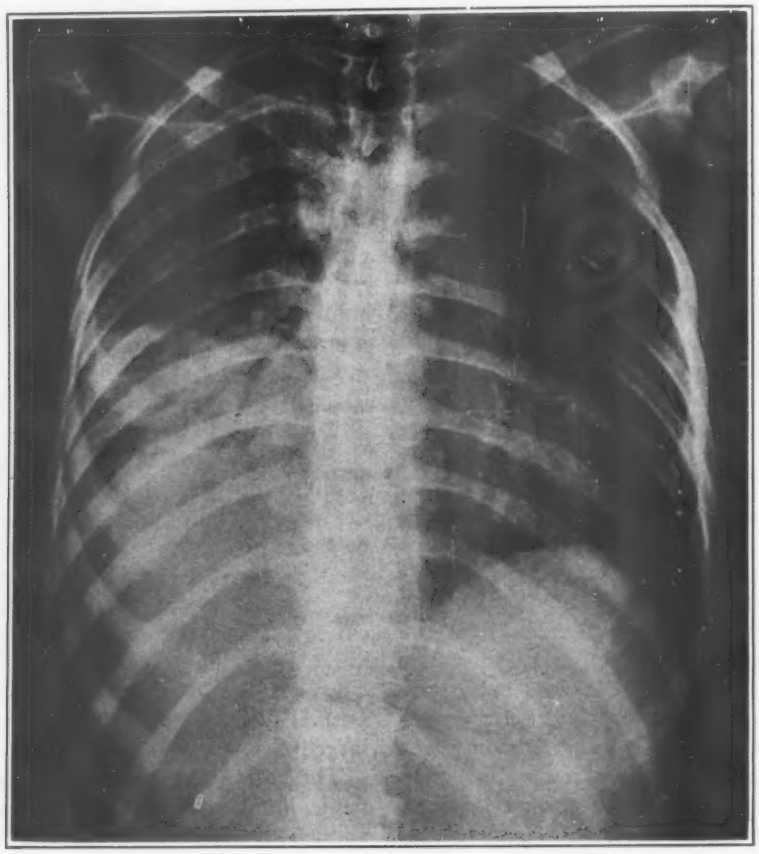

FIGURE 1.

DIFFERENTIAL DIAGNOSIS

DR. MARIAN ROPES: In this patient of twenty I think it is probably going to be necessary to make two diagnoses, possibly more. Some, or perhaps most, of the anatomic and physiologic changes are relatively apparent, but the etiology is much less obvious. During the first part of the disease the predominant feature was evidence of an ulcerative lesion of the colon. It is significant, however, that even at the onset, or soon thereafter, respiratory symptoms were apparent. If the attack of intestinal grippe marked the beginning of the disease, respiratory symptoms appeared at the onset. The first persistent symptom came some two months later and was wrongly diagnosed. The patient had blood in the stools; this was considered of little significance and was thought to have been due to hemorrhoids, which may or may not have been demonstrated. No further attempt was made to find the cause. Since she had diarrhea associated with the blood, it is even more surprising that no further search was made at that time. Shortly, however, the severity of the disease became apparent, and at the time of her first admission to a hospital the entire picture can be said to have been consistent with idiopathic ulcerative colitis, which appeared to respond rather well to treatment.

The first definitely atypical symptom was the attack of severe pain in the chest. Again, no attempt was made to determine the cause of the pain. It was treated with diathermy and apparently was of short duration. Both the gastrointestinal symptoms and the respiratory symptoms increased steadily, however, and at the time of the second admission to the outside hospital she had, in addition to a

persistent ulcerative lesion in the colon, definite evidence of pulmonary disease. The interpretation of the type of pulmonary disease is particularly difficult unless the density was greater than I assumed that it was; slight density over the entire chest is rather unusual if due simply to pleural effusion. The absence of a large pleural effusion seems to have been borne out by the fact that taps were unsuccessful. From that time until death the pulmonary disease increased rather steadily. Perhaps this is the best time to see the x-ray films.

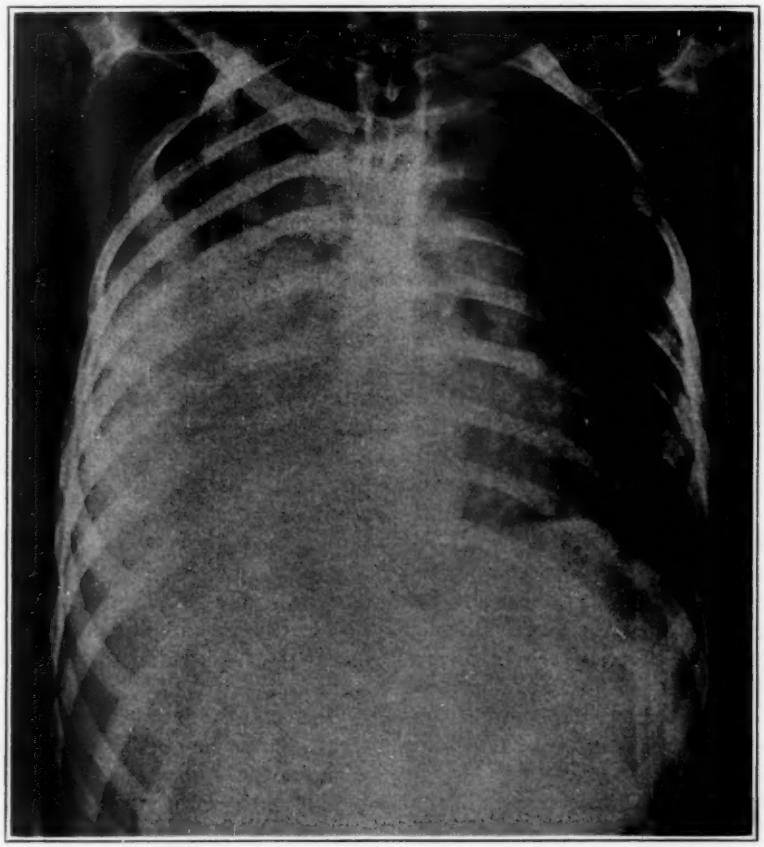

FIGURE 2.

DR. MILFORD SCHULZ: The film of the chest taken shortly after entry shows a densely consolidated area in the lower part of the right lung, in which there apparently is an abscess cavity. The miliary process throughout the lungs did not change much during her stay, but the whole right lung became denser, as recorded. It is curious that the bronchi within the consolidated lung contain air. The lung apparently was "drowned." The cavity is not apparent on the second film.

DR. ROPES: We have then two major processes — a severe ulcerative disease of the colon and a pulmonary lesion consisting of a miliary process, marked consolidation and probably cavitation. In addition, I believe that the cardiac findings indicate that the patient probably had rheumatic heart disease with mitral involvement, a sequela of the three attacks of rheumatic fever. Whether or not the attacks of pulmonary edema that came on acutely on several occasions during the last few days of her life were related to the underlying cardiac disease is impossible to say. It would be unusual to have these symptoms if cardiac failure were secondary to the pulmonary involvement. The question whether a rheumatic myocarditis was also present at that time cannot be answered, although it must be considered. Evidence of other systemic involvement is apparent. Hepatic dysfunction is indicated by several findings — the elevated van den Bergh, the high prothrombin time and the definite, although not marked, abnormality of the serum protein. The clubbing of the fingers could have been secondary to the ulcerative disease in the colon or to the pulmonary disease, possibly accentuated by both. The contractures of the legs are of interest. In general such flexion contractures rarely develop except in the presence of active joint disease or after prolonged immobilization. There was no immobilization in this case, but I hesitate to introduce an element of joint disease.

The case really comes down to the question

whether the pulmonary lesion and the ulcerative disease of the colon were due to the same etiologic agent, and if they were, what was the agent. The possibility that malignant disease was the explanation of this entire picture is extremely unlikely. On the other hand, various types of infection ought to be considered. One that is likely to give lesions of this type is tuberculosis. There are many unusual features, however. If the disease was primary in the lungs, which one must assume, the early onset of relatively severe colitis is unusual. The co-existence of a miliary process during the period of marked progression of the consolidation of the lobes is also atypical. Furthermore, the failure to find organisms is most unusual, although not impossible. Unfortunately, we are told the result of only one sputum examination. Possibly the patient did not raise sputum at any other time; but that is definitely unlikely because we know that early in the course of the disease she was raising sputum. The blood-cell counts and the differential are consistent with tuberculosis, but do not aid greatly in making the diagnosis. If the colitis was due to tuberculosis I should not expect a marked improvement during the early stage, with severe colitis thereafter. Again, this does not rule tuberculosis out, but it is unusual.

The possibility of parasitic infection must be considered, but I am unable to think of a parasitic or fungus infection to explain the whole picture. The one diagnosis that should possibly be considered is coccidiosis. The patient came from Oklahoma, which is included in the region where coccidiosis has been seen quite frequently. Coccidiosis can explain pulmonary lesions of this type. As I came into the room I asked Dr. Chester Jones whether he had heard of coccidiosis associated with ulcerative colitis. He said that he had not, but I wonder if this is one of the cases of diffuse involvement that are occasionally seen in this disease. The liver disease here might be ascribed to that.

In summing up the situation I shall conclude that the pulmonary lesions and the ulcerative disease of the colon were probably related. I expect that granulomatous lesions were found, perhaps not due to tuberculosis but possibly, although not likely, due to coccidiosis. Idiopathic ulcerative colitis in addition to the pulmonary disease is a possibility. I also believe that the patient had rheumatic heart disease with mitral involvement.

DR. CHESTER M. JONES: I saw this patient in the outside hospital before she was transferred here. She was a desperately sick woman at that time, and it was obvious that the chances of recovery were extremely slight. She had an ulcerative colitis that had progressed rapidly in spite of ileostomy, presumably done at the proper time. In addition she still had evidence of active ulcerative colitis, as indicated by diarrhea. She was markedly undernourished and greatly depleted, even after intensive treatment. We tried to cover the obvious deficiencies in various ways — vitamins, protein and so forth. The ileostomy was functioning but was surrounded by a sloughing area.

At that time the pulmonary situation was not apparent. My belief was that she probably had an idiopathic ulcerative colitis, because of the rather characteristic course. It started out as a relatively mild affair, with exacerbations and remissions, and then became much worse under conditions that were favorable for its progress. She was an extremely apprehensive person. She had been separated from her husband part of the time and the whole situation was difficult for her. Such a psychic background is a factor in ulcerative colitis and must always be taken into account.

When I examined her, there was tenderness in the flank, with slight rigidity. I thought that there was marked cellulitis of the bowel wall and was afraid that there might have been perforation. The prognosis appeared hopeless unless it was possible to take out the diseased colon, a major problem that could be done only as a desperate final move.

The experience with penicillin is of interest. During the last two years we have found that penicillin is of practically no value in ulcerative colitis. In one case that I have seen there was a brilliant result from its use, but in other cases there has been no favorable response.

The clubbing of the fingers was not unusual for this grade of chronic diarrhea, as Dr. Ropes has pointed out, although the mechanism of its production is not understood. The prolongation of prothrombin time is another common finding in serious diarrhea. We have seen two or three cases of infection in the liver itself as a result of ulcerative colitis, but it is rare. Enlargement of the spleen is not uncommon.

One point cannot be too heavily stressed: the treatment of hemorrhoids because of rectal bleeding without an adequate investigation must be avoided. I believe the rule still holds on the surgical service that a hemorrhoidectomy for bleeding is not permitted until sigmoidoscopy is done. Is that correct, Dr. Allen?

DR. ARTHUR W. ALLEN: Yes.

DR. JONES: That is a tremendously important dictum. This woman was treated for hemorrhoids because of the bleeding, when, as a matter of fact, the bleeding was due to ulcerative colitis. Experience has taught us that any local treatment tends to light up the disease.

I should doubt very much that these ulcers were tuberculous. The ulcerations of tuberculous colitis are usually sluggish, punched-out lesions with undermined edges. If one saw them in the rectum it would mean extensive disease, and in a severely ill patient one would expect the ulcerations to be typical. Here, apparently they were not. There was a large area of mucosa covered with pseudopolyps, with characteristic bleeding.

The joint disease is of interest. About 10 per cent of patients with ulcerative colitis have rheumatoid arthritis. It is an important finding, since it complicates treatment.

This case was hopeless from the beginning, but it seemed to me that we had to give her the benefit of the doubt and try to approach the problem from the point of view of potential colectomy. She was too serious a risk to tolerate major surgery. She died of pulmonary disease, accompanied by active colitis. I do not know anything about coccidiosis of the bowel. I suppose it can occur, but I have never seen a case. I am inclined to doubt that this was a case of coccidiosis of the lung and bowel.

Dr. Ropes: Did she have severe diarrhea in the hospital?

Dr. Jones: She had constant rectal discharge part of the time, but it let up. We have seen that with extensive involvement of the entire bowel. I was impressed that she did not have marked spasm of the abdominal wall.

Dr. Leland S. McKittrick: Dr. Jones mentioned the possibility and hope of a colectomy in this woman. This has been done in a certain number of desperately ill patients with success. Dr. Daniel F. Jones taught years ago that, if one is able surgically to remove the cause of the illness, the desperately sick patient will tolerate major surgery. In ulcerative colitis one of the basic principles in following out that dictum is the elimination of other conditions or complications, so that when colectomy is done the factor that has been making the patient sick is removed. When the lung condition became apparent in this patient, no attempt was made to remove the colon.

Clinical Diagnoses

Chronic ulcerative colitis.
Pulmonary tuberculosis?

Dr. Ropes's Diagnoses

Granulomatous disease of lungs (? coccidiosis, ? tuberculosis).
Ulcerative colitis (? coccidiosis, ? tuberculosis, ? idiopathic).
Rheumatic heart disease, with mitral involvement.

Anatomical Diagnoses

Pulmonary tuberculosis.
Miliary tuberculosis: lung, spleen, liver and kidneys.
Tuberculous peritonitis.
Chronic ulcerative colitis, idiopathic.
Rheumatic heart disease, with mitral stenosis.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy on this woman showed a diffuse process involving the entire colon up to the ileocecal valve; it was characteristic of the healing stage of idiopathic chronic ulcerative colitis. There were, as Dr. Jones mentioned, pseudopolyps with attempted bridging of the mucosa over the previously ulcerated areas. We found no evidence of acute ulcers in the colon; we took about a dozen sections and I could not find a really good ulcer, the epithelium having regrown over the ulcerations. The mucosa, submucosa and muscularis of the bowel showed nonspecific chronic inflammation but no evidence of any other process. The serosa of the bowel, both large and small, was studded with tubercles, so that there was a diffuse tuberculous peritonitis without ascites, which perhaps accounted for the pain and tenderness, as well as the slough around the ileostomy. The process in the lungs was due to active tuberculosis, and there was a miliary spread involving practically every organ of the body. I do not believe that there was any etiologic relation between the ulcerative colitis and the tuberculosis; that is, she had two separate diseases. I am confident that, if she had not developed tuberculosis, the ulcerative colitis could have been cured by colectomy, because it was not so severe a grade of colitis as we often see. Dr. Jones has asked me to hazard a guess concerning when the miliary spread started. I really do not know, but it might have been at the time she developed pain in the chest, about five months before admission.

Dr. Jones: What did the heart show?

Dr. Castleman: There was definite old rheumatic involvement of the mitral valve, with a moderate degree of stenosis but no evidence of activity.

A Physician: It might be worth while to mention that during the two weeks in this hospital there was practically no discharge from the rectum.

Dr. Castleman: That would fit in with our findings in the colon.

Dr. McKittrick: I should like to add a comment to what Dr. Jones said; that is, one cannot depend on the absence of rectal discharge or of diarrhea as evidence of a quiescent ulcerative colitis. I recently had a patient with a fever of 102 to 103°F. and a hemoglobin of 8 gm. or below over a period of weeks who had one formed, guaiac-negative movement a day. Ileostomy and later colectomy were necessary to cure the patient. What Dr. Jones says is correct. The essential thing is to exclude evidence of anything else that can cause fever, debility, anemia and so forth.

The house staff is to be congratulated for finding this pulmonary condition. It looks obvious in the x-ray films, but when you saw this young woman it was a different story.

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1945

The year of decision that was 1944 has joined the procession of the past, and the year of decision 1945 becomes our present and immediate future. Again we are faced with the promise of a credit of days to be put to use before the current annual allotment expires, and again we are confronted with certain goals that we hope to attain before the new year becomes another old one.

The year 1944, although one of decision, was certainly not our year of fulfillment. In 1944, it is true, we launched mighty offensives on land and sea, but the final decision is not yet in sight, and we have come to a realization of other facts associated with our great effort, to an appreciation of the possibility that war can bring us the extremes in human conduct — great sacrifices and great suffering on the one hand, and great selfishness and great indulgence on the other.

At a period when millions of our countrymen are putting in jeopardy their chief possession, and casualty lists are mounting, many thousands of others are maneuvering for a greater share of the restricted necessities of life, are bargaining for ignoble luxuries, are deserting essential industries and are strangers to that spirit of sacrifice without which a cause cannot be wholly won.

We will learn, in the year that we are entering, some useful and some chastening lessons. We will come with reluctance to a full appreciation of the fact that we are engaged in the most momentous and the bloodiest war of our history. We will realize, after three years in arms, that the early warnings of the experts were well founded, and that this time there is no easy road to victory, no slick trick by which the days of peace can be restored to us. We will be taught, perhaps in this year and certainly in the years to come, that the ending of war may bring practically anything but peace, for there can be no peace with cruelty, hatred and evil, or while there is still anything to fight for.

We will learn, by an experience that living generations have never yet encountered, that when a democracy goes to war it can win only with the full support of its people, that every individual must participate and that the extent and the speed of the victory are determined by the effort that is made. We may hope also that those in authority will finally learn that it pays to keep faith with the public, that in the long run truth pays better dividends than does propaganda and that any partnership must be based on mutual confidence.

Certain words of Paul to the Corinthians may be taken to heart also by all Americans, "He which soweth sparingly shall reap also sparingly; and he which soweth bountifully shall reap also bountifully."

CHEMOTHERAPY OF TUBERCULOSIS

Tuberculosis is one of the diseases that is usually considered as not being responsive to sulfonamide drugs. At present it is also being listed among the

conditions in which penicillin is ineffective. Because of the nature of this infection and its great prevalence, it is easy to understand why the lay press continually plays up any encouraging news concerning agents that possibly have a curative effect in the disease. If, however, such agents must be used for a long time and under conditions that are themselves not without danger to the health and life of the patient, such unwarranted publicity may cause considerable harm.

Many physicians throughout this country, particularly those interested in pulmonary diseases, have been considerably annoyed in recent months by the publicity given to one of the newer chemotherapeutic agents that is now being investigated in experimental tuberculosis and in human clinical cases. Indeed, the members of the American Trudeau Society, a group of eminent physicians with particular interest in the treatment of pulmonary tuberculosis, have considered this matter to be serious enough to warrant a special report by its Committee on Therapy. This report, which was presented at a meeting of the Medical Section of the National Tuberculosis Association on March 17 and 18, 1944, was published in the April issue of the *American Review of Tuberculosis*. It should serve to clarify the position of experts concerning the present status of the therapeutic agents under investigation. The following is quoted from this report:

> It is the opinion of the committee that the clinical and roentgenological data so far made available to the committee on the action of Diasone on human tuberculosis are as yet inadequate, both quantitatively and qualitatively, to permit, even tentatively, a positive evaluation of its curative effects upon tuberculosis in humans. The committee believes that there is, at this time, no adequate basis for the optimistic implications of the magazine articles or of the releases to the press which are now so well known to both the profession and public. It is believed, on the contrary, that such implications are distinctly unwarranted and not in accord with the clinical evidence which has been reviewed by the committee. The committee regrets exceedingly that the magazine articles mentioned previously were published in spite of efforts on the part of both the committee and the clinician to stop their publication.
>
> Until controlled studies of a definite scope have been reported, it is recommended that none of these drugs be used for treating tuberculous patients except under conditions which will appreciably add to our knowledge of their clinical action, and in the presence of adequate facilities to protect patients effectively from their potentially serious toxic effects. Patients and physicians must also be reminded of the provisions of the federal regulations which prohibit the distribution of a drug in the experimental phase of development to other than research institutions to which the material is assigned by the manufacturer for either laboratory or clinical investigation. The committee is informed that other clinical investigations are now in progress, and it is the expressed opinion of the committee that such further well-controlled clinical investigation is distinctly desirable.
>
> Any use of chemotherapeutic agents, including Diasone, in the treatment of tuberculous patients, must, therefore, be regarded as purely a project in clinical investigation. It must be again emphasized that such use is not without hazard and that the roentgenological and clinical evidence reviewed by the committee gives no justification at this time for any attitude concerning the value of these drugs in patients other than one of critical interest.

It is of interest that the same issue of the *American Review of Tuberculosis* contains a paper by Petter and Prenzlau, entitled "Treatment of Tuberculosis with Diasone," which was presented before the Mississippi Valley Trudeau Society in September, 1943. It is followed by a discussion by Dr. C. H. Hinshaw, who, interestingly enough, is the chairman of the Committee of Therapy of the American Trudeau Society. In his remarks, Dr. Hinshaw mentions several reports from Great Britain and the United States that suggest that Promin, another and similar chemotherapeutic agent, may have some therapeutic value. These reports, he adds, are encouraging, but he emphasizes that conclusive proof of efficacy in clinical tuberculosis is lacking for both Promin and Diasone. He also calls attention to the unpredictability of tuberculosis and to its marked tendency to heal without treatment, both of which, to be excluded, require rigid control. He also mentions studies carried out at the Mayo Foundation, which indicate that Diasone is less effective than Promin in experimental tuberculosis in guinea pigs. The Mayo workers also have found that both these drugs are more toxic to human beings than to guinea pigs. These toxic effects may be disturbing and even alarming, although they are usually controllable, unless there is an idiosyncrasy, by properly regulating the dosage. The slow rate of excretion of these drugs necessitates the greatest care in their use.

Petter and Prenzlau report observations on the use of Diasone in 44 patients with human tuberculosis who received an average of 0.9 gm. daily for an average of one hundred and fifty-six days.

They noted some degree of improvement in all the minimal and moderately advanced cases and in 79 per cent of far-advanced cases. Sputum conversion occurred in 59 per cent of all cases, and cavities closed during treatment in 43 per cent. They discuss the general reactions that were observed and emphasize the need for careful clinical and laboratory observations during the administration of the drugs. They believe that their findings point the way to further advances in the treatment of tuberculosis in man.

In a discussion in the May 26 issue of *Science*, under the title "The Paper Shortage and Scientific Publication," Griggs proposes early publication of abstracts or making promptly available in the form of microfilms all scientific papers as soon as they are received for publication. This, he feels, would serve the important purpose of acquainting scientists regarding the results of research by fellow workers. This, in turn, would help them in the conduct of their own studies and would have a tendency to reduce duplication of effort. So far as this discussion concerns scientific journals as a means of keeping research workers informed, there is much to be said in favor of these proposals.

Griggs goes on to stress the contributions of such abstracting magazines as the *Reader's Digest* to the field of literature. There is much to be said in favor of this argument. This type of magazine and other lay magazines may, in addition, render a useful service in popularizing some of the leading medical and scientific advances. It may not be entirely safe or desirable, however, to entrust these lay magazines with the premature announcement of great scientific discoveries in the field of medicine. Their function could best be served only after adequate and thorough discussion of the value of these discoveries by competent investigators in the field has proved beyond a doubt the value of the discoveries that they wish to popularize.

It is highly desirable that, in the future, such magazines try to avoid doing the disservice that has, in the past, resulted from rosy pictures prematurely painted concerning proposed remedies that are only in the process of being clinically evaluated. Such publication later results in serious disillusionment to the afflicted persons who seek relief, and not infrequently adds to their suffering, in addition to the considerable expense to which they may be put in the process.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

GRIMES — Warren P. Grimes, M.D., of Hillsborough, died November 13. He was in his seventy-seventh year.

Dr. Grimes received his degree from Harvard Medical School in 1891. He was a member of the New Hampshire Medical Society and the American Medical Association.

His widow survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Haverhill	January 3	William T. Green
Lowell	January 5	Albert H. Brewster
Salem	January 8*	Paul W. Hugenberger
Brockton	January 11	George W. Van Gorder
Pittsfield	January 15	Frank A. Slowick
Springfield	January 17	Garry deN. Hough, Jr.
Worcester	January 19	John W. O'Meara
Hyannis	January 23	Paul L. Norton
Fall River	January 29*	Eugene A. McCarthy

*Day changed.

NOTICES

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, January 4, at 7:15 p.m., in the classroom of the nurses' residence. Dr. Miriam G. Katzeff will speak on the subject "Postmenopausal Osteoporosis."

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, January 4

Friday, January 5

*9:00-10.00 a.m. Cancer of the Cervix. Dr. B. Lorincz. Joseph H. Pratt Diagnostic Hospital.

10:50 a.m. Benign New Growth. Dr. E. Lafreniere. (Postgraduate clinic in dermatology and syphilis.) Dowling Amphitheater, Boston City Hospital.

12:00 m.-1:00 p.m. Clinicopathological conference. Boston Floating Hospital. Held in Lecture Hall of Joseph H. Pratt Diagnostic Hospital.

Saturday, January 6

*10.00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, January 8

12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, January 9

*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

(*Notices continued on page xvii*)

NOTICES (*Continued from page 898*)

WEDNESDAY, JANUARY 10

*9:00-10:00 a.m. The Incidence of Psychoneurosis in the Medical Clinic. Dr. Joseph Kaplan. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Clinicopathological conference. Children's Hospital.

12:00 m.-1:00 p.m. Clinicopathological conference. Cambridge Hospital.

7:15 p.m. Graduate seminar in pediatrics. Children's Medical Service, Massachusetts General Hospital, Amphitheater 3A.

*Open to the medical profession.

JANUARY 3 to APRIL 25. Metropolitan State Hospital. Page 508, issue of October 5.

JANUARY 4. New England Hospital for Women and Children. Page 898.

JANUARY 11. Tropical Diseases (Particularly Malaria) as They Affect New England. Dr. W. C. McCarthy. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JANUARY 17. New England Society of Physical Medicine. Page xv, issue of December 21.

JANUARY 20 and 21. Forum on Allergy. Page 638, issue of November 2.

FEBRUARY 3. American Board of Obstetrics and Gynecology. Page 696, issue of November 16.

FEBRUARY 19. American Board of Internal Medicine. Page 436, issue of September 21.

MAY 22-24. Hotel Statler, Boston. Annual meeting of the Massachusetts Medical Society.

SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.

DISTRICT MEDICAL SOCIETIES

PLYMOUTH

JANUARY 18. Brockton Hospital, Brockton.
FEBRUARY 15. Jordan Hospital, Plymouth.
MARCH 15. Goddard Hospital, Brockton.
APRIL 26. Toll House, Whitman.
MAY 17. Lakeville Sanatorium, Lakeville.
All meetings will be held at 11 a.m.

WORCESTER

JANUARY 10. St. Vincent Hospital, Worcester.
FEBRUARY 14. Worcester State Hospital.
MARCH 14. Worcester Memorial Hospital.
APRIL 11. Hahnemann Hospital, Worcester.
MAY 9. Annual meeting.

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Rachitic changes were present as late as the fourteenth year, and the incidence was higher among children dying from acute disease than in those dying of chronic disease.

The authors conclude, "We doubt if slight degrees of rickets, such as we found in many of our children, interfere with health and development, but our studies as a whole afford reason to prolong administration of vitamin D to the age limit of our study, the fourteenth year, and especially indicate the necessity to suspect and to take the necessary measures to guard against rickets in sick children."

*R. H. Follis, D. Jackson, M. M. Eliot, and E. A. Park: Prevalence of rickets in children between two and fourteen years of age, Am. J. Dis. Child. 66:1-11, July 1943.

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